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Review

Anti-inflammatory, antithrombotic and anti-oxidant bioactives of beer and brewery by-products, as ingredients of bio-functional foods, nutraceuticals, cosmetics, cosmeceuticals and pharmaceuticals with health promoting properties

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Abstract: Fermented alcoholic beverages and their by-products, including beer and breweries' bio-wastes like spent yeasts, grain, and hops, contain a plethora of natural bioactive compounds that have recently gained attention for their valorization as functional ingredients in several novel foods and nutraceuticals, as well as in drugs and cosmetics applications. Within this article, the natural bio-functional compounds of fermented beer product and breweries' by-products with anti-inflammatory, antithrombotic, and anti-oxidant bioactivities are thoroughly reviewed. The important roles of yeasts involved for such bioactives to be present in the fermented product and in the brewery bio-wastes are also outlined. The health promoting benefits of beer moderate consumption resulting from these bioactives, as part of a balanced diet, against inflammation-related chronic disorders is also discussed, along with the detrimental effects of beer consumption abuse and the potential benefits of alternative non-alcoholic beers. The mechanisms of action and synergism of the natural bioactives present in the fermented beer product and in breweries' by-products, with anti-inflammatory, anti-thrombotic, and antioxidant properties are also presented. Current research and future perspectives on valorizing bioactives of fermented beer and brewery by-products, such as spent yeasts, grain and hops in health-promoting functional foods, supplements, nutraceuticals cosmetics, cosmeceuticals, and

pharmaceuticals are also thoroughly evaluated, while the limitations of their use are also discussed.

Keywords: beer; brewery by-products; fermentation; hops; spent grain; yeast; polyphenols; lipid bioactives; anti-inflammatory; health benefits

1. Introduction

Beer and other fermented alcoholic beverages have been consumed lavishly since antiquity [1], and nowadays it is well-known that moderate beer consumption could be beneficial due to its bioactive compounds, namely phenolics, pre-/pro-biotics, and lipid bioactives [2–4]. Inflammatory-linked chronic disorders lead to global challenges, while lifestyle and diet patterns significantly affect them [5–7]. Thus, foods and/or food by-products rich in bioactive microconstituents, with potential health benefits, i.e., apple cider, beer, wine and so on, has attracted the interest of society and scientists [2,3,8–10].

Beer is ranked fifth among the world's most popular fermented beverages, while it is the most consumed alcoholic drink globally [2]. Beer production is a rather easy process, based on the fermentation of sugar wort and is composed of various components, including water, hops (*Humulus lupulus*), malted barley (*Hordeum vulgare*), and brewer's yeast (strains: *Saccharomyces cerevisiae* and *Saccharomyces pastorianus*) [2,3,8].

Beer has a long tradition of being utilized for various therapeutic purposes [2,3,8], and the sensory and textural characteristics along with the nutritional value of beer are significantly affected by its bioactive compounds [2,3,8]. A variety of bioactive compounds, namely lipids, phenolics, iso-alpha acids, and prenyl-flavonoids and their metabolites [8,9,11], are found in beer and in the by-products of breweries, originating from the raw ingredients from several biochemical modifications during brewing. Additionally, various bioactive compounds emerged from the yeast fermentation and brewing process, encompassing bitter elements, volatile esters, and melanoidins [12,13]. Flavonoids are the most studied beer bioactives [2,3,8], while beer phenolic compounds and prenylated flavonoids, such as the hops-derived xanthohumol and humulone, promote well-being and prevent inflammation and insulin resistance, as well as demonstrate antitumor and chemopreventive effects [3,8,14–18]. Additionally, beer's bioactive lipids demonstrate potential anti-inflammatory and antithrombotic properties against established factors in thrombosis and inflammation, including thrombin and platelet aggregating factor (PAF) [8,11,19].

On the other hand, excessive beer intake has been linked to several pathologies [2,8], suggesting a J-shaped curved association of beer consumption with overall mortality, while epidemiological studies have pointed out that even low to moderate beer consumption may be linked to an increased risk of overall mortality, ischemic heart disease, cancer, and cerebrovascular disease [2,9,20,21].

A comprehensive evaluation of the existing literature regarding beer and its bioactives is diligently undertaken in the present review. This includes a detailed exploration of the nutritional content, bioactive compounds, and potential protective effects linked with this fermented alcoholic beverage, emphasizing its moderate consumption as part of a healthy diet. The detrimental effects of beer abuse on health are also discussed, as well as the potential of non-alcoholic beer products as substitutes with proposed health benefits in the absence of alcohol.

Additionally, the bio-functional compounds present in beer by-products are also of interest, as they all can be reused within the food, cosmetic, and pharmaceutical sectors. The primary by-products consist of brewer's spent grains (BSG), spent hops (BSH), and surplus yeast (BSY), while among these BSG accounts for the largest amount, comprising 85% of the total. In contrast, BSH and BSY constitute 5% and 10% of the total by-products, respectively. Additionally, they retain relatively high moisture content, since approx. 20% of the water used in the brewing process remains in the residual material [22,23].

Beer is a globally consumed beverage, while Europe is its main consumer (40% of total alcohol consumption) [24]. Differences in beer brewing production techniques and ingredients lead to different and unique flavors and beer qualities [8]. According to some authors, the beer production process is a well-established general method that is categorized into three primary stages: substrate preparation, fermentation, and maturation with several additional sub-steps [25]. Nevertheless, alterations in the methods applied produce different beer products with unique chemical composition and sensory and functional characteristics and compounds. Subsequently, brewery by-products also display variations in composition, moisture, ash content, and nutritional value, depending on the ingredients used, the fermentation parameters, and the overall method applied.

Within this article, the health effects of beer and its bioactives, as well as the increasing interest for the recovery of bioactive compounds from brewery by-products, aiming to utilize them as functional ingredients or as raw materials/substrates for the production of novel functional products, including foods, nutraceuticals, cosmetics, cosmeceuticals and pharmaceuticals, with potential health-promoting properties, will be thoroughly evaluated.

2. Beer and breweries' by-products content in bio-functional compounds

2.1. Beer composition

Water is beer's primary ingredient (approx. 90-96%), while the alcohol by volume (ABV) in alcoholic beers ranges from 4–6% depending on the type of beer. Carbon dioxide dominates the remaining constituents, while several bioactive macro- and micro-constituents are also present in beer [8,12,19]. Additionally, the energy content of beer is primarily attributed to carbohydrates (4 kcal/g), amino acids (4 kcal/g), total organic acids (4 kcal/g), and alcohol (7 kcal/g) [12]. As for the macronutrients, beer generally contains a relatively low amount of protein (5% ABV beer contains approx. 0.5 g protein/100 mL) [12]; carbohydrates, namely monosaccharides, oligosaccharides, arabinoxylans, beta glucans, and dextrins, represent 3.3–4.4 g/100 mL beer [12]. Lipids, such as fatty acids and polar lipids, are present in beer, albeit in small quantities, with diverse types and levels [8,11,12,19]. It is worth mentioning that the main source of lipids in beer is barley (approx. 2–4%), while malt contributes around 3.4% of lipids [11,19].

Additionally, hops represent a key factor in preserving beer and contributing to its bitterness and bioactive compounds. This is achieved primarily through hydrophobic hop-derived α-acids, such as humulone and its derivatives, and β-acids, including colupulone and lupulone among others [26–28]. These bioactive bitter acids not only influence the quality and flavor of beer, but also exhibit antioxidant, anti-inflammatory, and potentially chemopreventive properties [12].

Apart from these hop derived bioactives, beer also contains several polyphenols, aldehydes, esters, and ketones, which vary based on the ingredients and processing methods employed, while beer

also contains vitamins and minerals, too [3,8]. Furthermore, beer yeasts play a functional role in this alcoholic beverage since they can positively affect health due to their ability to convert wort phenolics into healthier compounds, namely melatonin and/or hydroxytyrosol, while at the same time they may act as potential probiotic agents [29].

2.2. Composition of breweries' by-products

2.2.1. Brewer's Spent Grains (BSG)

Brewer's spent grains (BSG) are the main by-products of beer production (571pprox.. 85% of the total by-products); BSG mainly consist of barley husks and residual endosperm starch granules. The composition of BSG varies due to variety, grinding level, malting, and glycolysis conditions. BSG are mainly sources of dietary fibers (they contain 60–71% soluble dietary fiber) [30], namely arabinogalactans, β-glucans, pectic polysaccharides, branched arabinoxylan, and xyloglucans, while the insoluble dietary fiber fraction consists of arabinoxylan (AX), cellulose, galactomannans, lignin, and xyloglucans [22,31,32]. In addition, BSG also contain compounds that make them suitable sustainable resources for functional products' production, namely essential amino acids, vitamins, minerals, and polyphenols (Figure 1) [22,33,34].

2.2.2. Brewers Spent Hops (BSH) and Trub

Hops (*Humulus lupulus L.*) are a herbaceous, perennial, and dioecious plant, mainly cultivated in North America and Europe for its use in beer production. However, only 15% of the hops initially added in the brewing process are still present in the final beer product, resulting in a huge amount (85%) of remaining BSH. Dried hops and BSH are mainly composed of fiber, with additional compounds like bitter acids and proteins. Even though BSH are sources of carbon, nitrogen, and protein, their bitter taste makes them almost unsuitable for direct consumption [35]. Hops mainly contain mono- and di-saccharides, namely galactose, glucose, mannose, and xylose, while arabinose, pectin, rhamnose, and uronic acid are also present in lower amounts [22]. The discarded hops are called "hot trub" and it represents the sediments that amass during the boiling of wort in the brewing process; these heated particles size ranges from 30–80 μm, while such residue primarily comprises colloidal proteins (40% to 70%) that form complexes within the wort by naturally binding with polyphenols present in the liquid phase [22,36].

2.2.3. Brewers Surplus Yeasts (BSY)

BSY represents the second most abundant by-product of beer production (10% of the total by-products) [22], while such residue is gathered from the fermented and matured product via sedimentation, since they can only be used through this cycle a maximum of six times. BSY primarily consists of proteins (45%–55%) and saccharides [23], while the BSY protein's composition is almost the same as that of BSG and BSH, especially regarding essential amino acids, namely alanine, glutamine, and glutamic acid followed by similar vitamin and mineral contents. Yeasts also contain rather significant amounts of polyphenols, B-group vitamins, and minerals. Thus, these are being more commonly employed in animal feed and dietary supplements [37]. The mineral residue of BSY varies

depending on its source (2%–8.5%), while the dominant minerals are sodium and potassium. Centrifugation or sedimentation techniques can be used to reclaim BSY, since the resulting sediment usually comprises 12–16% dry matter. In order to reuse the BSY, a prolonged storage step should be applied; for this purpose, yeast biomass should be refrigerated or preserved through lyophilization, pasteurization, or spray drying, while the isolation of BSY extracts, containing bio-functional compounds, may also take place. Thus, procedural aspects, namely pH levels, reaction duration, and sterilization conditions, are key factors in preserving elevated levels of such constituents [38].

2.3. Beer and breweries' by-products' polyphenols; mechanisms of action and health promoting properties

2.3.1. Beer bioactive phenolics; health promoting effects and mechanisms of action

Beer contains a variety of bioactive phenolics, mainly flavonoids [8], which act as potential health promoting agents [8,24]. Hops gives approx. 30% of beer's polyphenols, while the remaining 70% emanate from barley malt and undergo chemical reactions during brewing [24]. The kind and the amounts of phenols may vary among different beer types [12], while their composition encompasses several different groups, including flavanols, flavones, phenolic acids, simple phenolic alcohols, and tannins [9]. Phenolic bioactives play a crucial role in the antioxidant activity of beers, while maintaining the flavor and the frothing of the beers, too.

Hops harbor numerous bioactive micro-constituents that are transferred to the finished beer, including isohumulone, xanthohumol, and their counterparts isoxanthohumol, 8-prenylnaringenin, and 6-prenylnaringenin, as well as alpha-humulene, beta-caryophyllene, and sesquiterpenes [28,39]. Only 25% of hops' metabolites, such as the α-acids adhumulone, cohumulone, and humulone, are preserved in beer as they undergo isomerization into more water-soluble iso-α-acids during the wort boiling process [26,28]. In addition, UV radiation, temperature, and pH can also lead to isomerization of hops' β-acids too, such as lupulone, colupulone, adlupulone, prelupulone, and postlupulone, during the brewing process [28], while when exposed to oxygen, both α- and β-acids can be transformed into various hulupone derivatives too. During storage, hulupones break down into a non-bitter substance called hulupinic acid.

Beer iso-α-acids, also known as isohumulones, which are formed during the beer production process through the isomerization of hop α-acids or humulones, along with matured hop bitter acids (MHBAs), contribute to the hop-derived bitter components of beer [40], while even they are present in beer at significantly low concentrations (3.3–64.0 mg/L and 19.1–210 mg/L) [41]. The iso-α-acids have been extensively studied for potential health benefits, such as obesity prevention, alleviation of menopausal symptoms, and antioxidant and anti-inflammatory properties [42].

Concerning the mechanisms of action of such beer and hops phenolic bioactives, it has been found that they can inhibit the production of inflammatory mediators, including prostaglandin E2 (PGE2), when assessed via metabolomics and *ex vivo* anti-inflammatory assays [43]. Additionally, encapsulating hop extracts rich in oxidized bitter acids within rapeseed lecithin nanoliposomes has enhanced their anti-inflammatory effects against the IL-1β inflammatory pathway in chondrocytes, demonstrating their potential benefits against osteoarthritis [44]. Moreover, the consumption of hop bitter acids has been associated with improvements in object and spatial recognition memory functions, along with increased dopamine levels in the hippocampus through vagus nerve activation [45].

Xanthohumol is a hops-derived bioactive, and its mechanisms of bioactivities and associated health benefits have been thoroughly studied [46,47]. These include its inhibitory effects against angiogenesis and inflammatory signals, suppression of metabolic activation of procarcinogens, and the impeding of the early stages of tumor growth [14]. Additionally, xanthohumol induces apoptosis through both intrinsic and extrinsic pathways, promoting cell cycle arrest and cancer cell death [47]. Several studies have demonstrated that, even at low concentrations (40μm), xanthohumol can induce cell cycle arrest and reduce cell viability at the G2/M phase in various cell lines, while according to others, such compound may activate the MAPK JNK pathways, facilitating apoptosis in nasopharyngeal carcinoma [48].

Several other health benefits have been attributed to xanthohumol, since it was found to possess anti-obesity and anti-neurodegenerative activity, as well as beneficial roles in reducing inflammation caused from osteoarthritis, hepatoprotective properties, ability to minimize tumor-related proteins and enzymes, and positive effects on intestinal tract function [15,17,18,47,49,50], while according to others, a dietary supplement containing 1.35–2.50 mg xanthohumol/kg/day may be necessary to achieve its desired pharmacological results [47]. Even though there are a plethora of *in vitro* studies revealing the potential health benefits of xanthohumol, in vivo studies have also been conducted with respect to the safety, tolerability, and efficacy of xanthohumol consumption in both animals and humans [46]. Even though xanthohumol may constitute approx. 1% of the dry weight of hop cones, its presence in wort and beer is typically lower due to its hydrophobicity [42], since it undergoes isomerization and transformation into isoxanthohumol during hop boiling [42]; isoxanthohumol shares similar health-promoting properties with xanthohumol, including anti-inflammatory and antioxidant attributes [16,42,51,52], while, additionally, it may possess antimicrobial and antidiabetic properties and exhibits greater stability in beer than xanthohumol [16,53].

According to Mahli et al., the use of micellar solubilized xanthohumol effectively countered the weight gain and glucose intolerance induced by a Western-type diet (WTD), while this compound significantly reduced activation of hepatic stellate cells (HSC), immune cell infiltration, hepatic steatosis, pro-inflammatory gene expression (MCP-1 and CXCL1), and collagen alpha I production in the livers of WTD-exposed animals [54]. Additionally, Dorn et al. found that xanthohumol could reduce liver inflammation and fibrosis in a mouse model of nonalcoholic steatohepatitis, suggesting that its protective effects in toxic liver injury are due to its ability to mitigate both hepatic inflammation and hepatic stellate cell activation [55]. In another study, xanthohumol, among others, provided protection against acute liver damage induced by carbon tetrachloride (CCl_4) in rats [56]; xanthohumol has demonstrated an ability to inhibit the proliferation of specific types of cancer cells since it exhibited significant suppression of proliferation and NF-kB activation in pancreatic cancer cell lines [57]. The research also revealed that xanthohumol reduced angiogenesis by inhibiting NF-kB and its downstream targets, leading to the inhibition of angiogenesis even at low concentrations [57]. Given that low-dose xanthohumol did not interfere with normal physiological functions, it is plausible that utilizing the natural product xanthohumol could be a safer and less toxic alternative to other treatments.

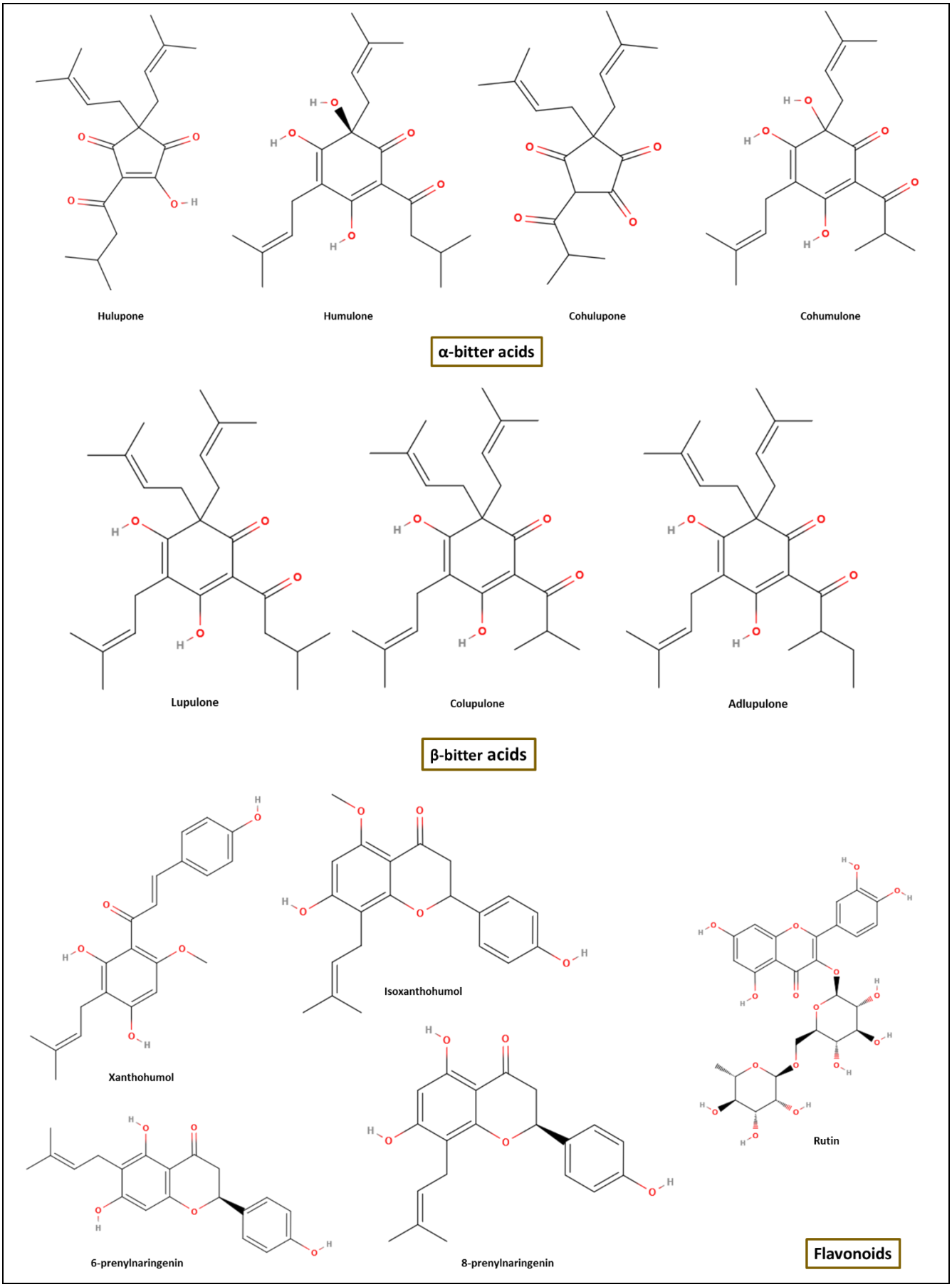
Beer phenolics had a favorable impact on blood pressure and might reduce the risk of cardiovascular diseases by increasing the concentration of nitric oxide in the bloodstream [12]. Furthermore, beer polyphenols undergo transformations, leading to the formation of various metabolites during the process of digestion; for instance, beer contains tyrosol, a simple phenolic compound that originates from the metabolism of tyramine during beer fermentation and can convert into hydroxytyrosol, a potent antioxidant with an increased ability to neutralize free radicals due to the

presence of an additional OH group [58]. Overall, beer content in bioactive polyphenols has been associated with the beneficial effects of moderate beer consumption [2,3,8,16]. Worth noting, craft beers have demonstrated significant antioxidant properties, attributed to their elevated phenolic content, which range varies between 343.8 and 2172.5 mg gallic acid equivalents (GAE)/L and significantly exceeds the one of the industrial beers [59].

2.3.2. Brewery by-products' bioactive phenolics; health promoting effects and mechanisms of action

Brewery by-products, namely BSG and BSH, are rich in phytochemicals, including phenolic acids (Figure 1). Polyphenols of brewery by-products are mainly derived from barley (70–80%) and hops (20–30%) [22], while some specific phenolics present in hops create complexes with wort proteins during the cooling phase; such complexes precipitate and are removed during filtration in the respective brewing process stages, leading to an extra contribution of phenolic compounds to the beer brewing by-product phenolic content [22]. Bioactive phenolics demonstrate antioxidant capacity, and thus they play a vital protective role in the body against the oxidative stress and the accompanying reactions, diminishing the risk of chronic diseases [22].

It is worth mentioning that such compounds can be extracted from brewery residuals and reused as functional ingredients in several applications. The plethora of bio-functional phenolics present in brewery by-products provides a variety of mechanisms of actions of their health promoting properties. For example, phenolic acids, namely hydroxybenzoic acids (HBAs) and hydroxycinnamic acids (HCAs), are commonly found in brewery by-products, and they are well-known for their antioxidant, anti-inflammatory, and anticarcinogenic effects [60], derived from their ability to affect and thus beneficially regulate the NF-kB signaling. The anti-neoplastic properties of phenolic acids against various cancer cell lines, namely adenocarcinoma, breast cancer, cervical cancer, and lymphoblastic leukemia, are also associated with a decrease in the expression of COX-2 that is an inflammatory-linked enzyme (conversion of arachidonic acid into prostaglandins) and the development of cancer. Additionally, one of the characteristics of apoptosis, namely DNA fragmentation, was reduced when cells were pre-treated with phenolic acids prior the exposure to H_2O_2 [60]. Specifically, caffeic acid prevented externalization of the phosphatidylserine, indicating its potential anti-apoptotic effect, while McCarthy et al. showed that spent grain extracts significantly reduced DNA damage caused by H_2O_2 [60]. Ferulic acid is also associated with protective effects against coronary disease, improvements in sperm quality, and reductions in serum cholesterol levels, while both ferulic and p-coumaric acids acted as precursors for the biocatalytic production of valuable aromatic natural compounds [33]. Furthermore, increased levels of p-coumaric acid have been found to increase DNA damage induced by H_2O_2, resulting in the generation of reactive oxygen species. As for resveratrol and other phenolic compounds, including flavones, they presented in brewery by-products in significant amounts and they demonstrate cardioprotective and anti-inflammatory activities; such compounds can prevent platelet aggregation [8,10,60,61], while at the same time, they led to the reduction of the production of platelet-activating factor (PAF), leading to a decrease in the overall inflammatory response [62,63]. The ability of these bioactive compounds to lower the levels and activity of thrombo-inflammatory mediators, namely PAF and thrombin, is rather promising against chronic diseases [6–8,10,61–63].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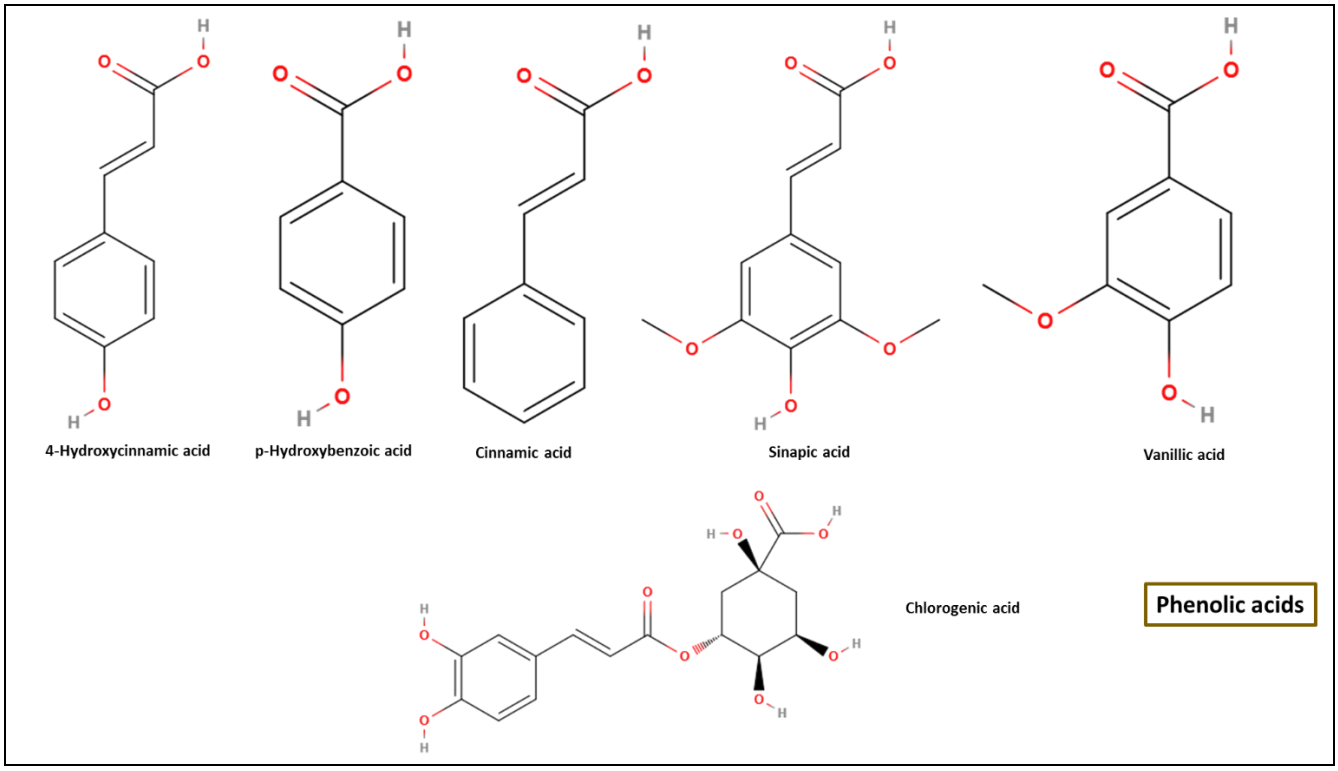

Figure 1. The structures of the main phenolic bioactives present in beer and brewery by-products, such as BSG, BSH, and BSY, i.e. α-bitter acids, β-bitter acids, flavonoids, and phenolic acids. Structures were obtained from https://molview.org/ (assessed on 12th of April 2024). BSG: brewers spent grain; BSH: brewers spent hops; BSY: Brewer's surplus yeast.

BSG presents a promising secondary product along with a cost-effective source of bioactives, with barley husks being the main repository of phenolics, including hydroxycinnamic acids presented in the cell walls. Given the fact that there is a trend to reduce synthetic additives and to use bioactives from sustainable environmentally friendly sources with potential antioxidant and antimicrobial properties, BSG is a rather ideal option for such a bioactives' source [22,64]. The phenolic content of BSG may vary due to the different barley variety used, the presence of husks, the malting conditions, and the specific extraction applied. BSG phenolic content is usually within the range of 2.1–9.9 mg gallic acid equivalents (GAE)/g, while total flavonoid content ranges from 0.02 to 4.6 mg quercetin equivalents (QE)/g, depending on the solvents used during the extraction [22], while BSG contains 1.1% of monomeric and dimeric phenolic acids, with ferulic acid and p-coumaric acid (p-CA) being the dominants, followed by p-hydroxybenzoic acid, sinapic acid, caffeic acid, vanillic acid, and syringic acid; ferulic acid amounts ranging between 1860–1948 mg/g, being approx. 53% of all monomeric phenolic acids in BSG, while p-CA amounts were between 565–794 mg/g [32,65].

Several studies have evaluated the extraction of phenolic acids from BSG, using diverse techniques, including liquid-liquid and liquid-solid extraction, employing solvents, namely methanol or ethyl acetate, applying acid hydrolysis, and saponification with NaOH, while some innovative extraction methods, namely fast microwave-assisted derivatization, have also been investigated. Alkaline hydrolysis recovered ferulic acid from spent grains yields a 0.3% recovery, while the addition of esterases derived from sources cultivated on spent grains has enhanced the release of ferulic acid

from BSG by approx. 3.3%. Additionally, crude *Fusarium oxysporum* use has led to an increase of ferulic acid content of BSG and β-glucanase sourced from *Humicola insolens* has proven effective in liberating ferulic acid from BSG. Microwave Assisted Extraction (MAE) has also been employed to extract phenolic compounds from BSG [64]. The extraction method significantly affects the phenolic content observed, while the presence of numerous esterified phenolics into BSG's lignocellulosic matrix was an extra extraction challenge [32].

It is worth mentioning that supercritical CO_2 has also been applied for the extraction of polyphenols from BSG, and this method, along with microencapsulation, can mask bitterness when foods are enriched with such compounds, while at the same time it helps to stabilize the polyphenols extracted from BSG; in addition, microencapsulation is employed to enhance the sensory attributes and appearance of BSG during the preservation of the bioactives derived from it, while this approach makes spent grain extracts more convenient for use in food products since they manage to retain their beneficial properties [23].

Not only the extraction process, but also the fractionation process of rich in phenolics BSG extracts, affects the content of the fractionated phenolics and their pharmacological bio-functionality. For example, polyphenol-rich BSG extracts, which were generated using 60% acetone and 0.75% NaOH solutions, were further subjected to liquid–liquid partitioning using various organic solvents, and the most abudant in phenolics diethyl ether fraction of the saponified BSG extract inhibited both acetyl- and butyryl-cholinesterases, with caffeic acid presenting the highest inhibition for both cholinesterases, suggesting potential as natural anti-cholinesterase agents of the polyphenol-rich BSG fractions against neurodegenerative disorders and brain tumors [66].

Apart from BSG, hops are also a rich source of bioactive phenolics, as they are extensively cultivated primarily for their secondary metabolites, namely xanthohumol and the α- and β-acids, which are used in brewing to impart bitter flavors and aromas to beer [39]. Prenylflavonoids, particularly xanthohumol and dexmethylxanthohumol, have been the primary focus of research in the context of beer and hops. Hops phenolics are molecules with high weight, such as tannins, while they also include glycosylated compounds (20% of the total hops polyphenols) [39].

Dominant secondary compounds found in hops, including bitter acids and volatile oils, are retained in brewery by-products as a result of the brewing process. Hop bitter acids are categorized into two groups: α-acids (e.g., humulone) and β-acids (e.g. hupulone), while they are both derivatives of prenylated phloroglucinol, and their composition and concentrations depend on the hop variety and growing conditions [22]; α-acids contribute approx. 80% of the beer's bitterness [22], while 75% of α-acids remain in BSH and BSY. Specifically, BSH contains approx. 8017 μg/g of bitter acids, while BSY contains around 1130 μg/g [67]. The main α-acids found in hops are cohumulone, humulone, and adhumulone, constituting approx. 35–70%, 20–65%, and 10–15% of all α-acids, respectively. It is worth noting that during fermentation, hop-derived microconstituents, including xanthohumol, α-acids, and β-acids, can undergo isomerization to become isoxanthohumol or iso-acids, and such compounds are also found in both BSH and BSY. When excess yeast is exposed to oxygen after or during the extraction, this results in the presence of various β-acids, namely hulupone and its derivatives in BSY [67]. BSY also contains significant amounts of several other bioactive phenolic compounds too, which are present in beer and hops due to being absorbed from malt and hops during the brewing process. For example, Vieira et al. identified 13 phenolic compounds in yeast, including caffeic acid, (±)-catechin, chlorogenic acid, cinnamic acid, (−)-epicatechin, ferulic acid, gallic acid, isoquercetin, p-coumaric acid, protocatechuic acid, rutin, syringic acid, and vanillic acid [68].

Since such bioactives, including xanthohumol, isoxanthohumol, and several other bitter acids of hops that are also present in BSH and BSY, have exhibited a wide range of anti-inflammatory actions, such as reduction of expression of inflammatory prostaglandins (i.e. PGE2) and cytokines through inhibition of NFkB activation, reduction of liver inflammation and hepatic fibrosis, increased antioxidant enzyme activity and glutathione levels in the liver, scavenging of reactive oxygen species and reduction of oxygen levels caused by ischemia-reperfusion injury [22], as well as anti-cancer potential, this further suggests that these bioactives, if appropriately isolated from brewery by-products, can be utilized as anti-inflammatory compounds for the development of novel bio-functional products in a circular economy design [22,69].

2.4. Beer and brewery by-product lipid bioactives; health promoting effects and mechanisms of action

Malted barley is beer's primary source of nutrients, since it contains up to 4% lipids DW, even though commercially available malts may have lipids up to 3.4% [8]. Lipid content decreases during the germination and mashing due to the release of fatty acids from triglycerides through hydrolysis [19], and thus a significant loss of lipids take place during these processes, with the final beer product containing less than 0.1% lipids [8,19]. The composition of fatty acids and lipids are affected by several factors, namely barley variety, malting process conditions, and lipid metabolism in yeast during brewing [19,70,71].

The significance of lipids within beer fermentation and their effect on the ability of the brewing yeasts to block potentially toxic effects of ethanol have been recently published [70]. Lipids and lipid droplets may regulate biological processes linked to ethanol tolerance, namely autophagy and proteostasis; therefore, their biosynthesis is necessary for yeast ethanol tolerance [70]. The presence of lipids in wort and in the beer is of significance since they are vital compounds in yeast growth, metabolism, and the foam stability of beer [12], while yeasts create and reform a range of lipid varieties, namely phospholipids and polyunsaturated fatty acids (PUFAs) [12]. Additionally, yeast strains have the ability to produce medium-chain fatty acids, namely octanoic acid and decanoic acid, with different impacts on beer characteristics, resulting in both desired and undesired sensory attributes [12]. Lipids presence in the final beer product is generally undesirable due to their negative effect on sensory characteristics [71], while beer foam stability, known as 'krausen', is a critical beer quality parameter and may be affected by the presence of fatty acids, too [8].

Various beer varieties, namely stouts, ales, and lagers, are gaining the interest of scientists due to the existence of bioactive polar lipids in the fermentation by-products [11,19,72]. Polar lipids (PLs) are a class of lipids with hydrophobic hydrocarbon residues and a hydrophilic group, such as a phosphate head or carbohydrate group [11]. PLs primarily provide structural support to cell membranes, while several PLs possess additional biological functions related to cell signalling, digestion, and inflammation [7]. The anti-thrombotic and anti-inflammatory properties of beer PLs have been recently reported, suggesting potential health benefits when beer is consumed in moderate amounts [8,11], while studies on red wine and olive oil have demonstrated that polar lipids act as protective agents against the development and growth of inflammation-related disorders, namely atherosclerosis, cancer, and cardiovascular disease (CVD) [6,7,10,73].

Thus, lipid composition, especially in ales, is a key factor in the potential health effects associated with beer consumption [8,11], while various beer types (ales, stouts, lagers), contain, among other things, bioactive PLs that may act as potential anti-inflammatory and anti-thrombotic compounds against

thrombo-inflammatory mediators such as thrombin and platelet-activating factor (PAF) [11,19,72]. Even though beer contains low amounts of lipids, these PLs seem to exhibit remarkable bioactivity, even in such limited quantities, and demonstrate potent inhibition of human platelet activation [11,19,72]. Subsequently, the co-presence in beer of both bioactive PLs, with beneficial effects against thrombo-inflammatory manifestations, and phenolics, with antioxidant and anti-inflammatory properties, further support the health promoting properties associated with moderate beer consumption [11,19,72].

In terms of structural elucidation, by using GC-MS and LC-MS lipidomics, it has been found that the bioactive PLs in Irish ale were mainly its phosphatidylcholines (PC), phosphatidylethanolamines (PE), and several sphingomyelin (SM) derivatives [11], all of which had a rich content in monounsaturated fatty acids (MUFAs), namely oleic acid (OA; 18:1 c9) and palmitoleic acid (16:1 c9), along with polyunsaturated fatty acids (PUFAs), namely omega-6 (n6) linoleic acid (LA; 18:2n6) and omega-3 (n3) α-linolenic acid (ALA; 18:3n3) [11], while traces of the long-chain n-3 docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) were also detected (Figure 2) [19]. Moreover, LC-MS also revealed the presence of glycolipids and sphingolipids in ale, including ceramides, cerebrosides, and glycol-sphingolipids, which further elucidate the health benefits associated with beer consumption [11]. Low ratios of n-6/n-3 polyunsaturated fatty acids is a characteristic of healthy diets and has been associated with several anti-inflammatory benefits [74], while such unsaturated fatty acids (UFA) possess on their own strong anti-inflammatory potential. The presence of bioactive MUFA and PUFA into beer PLs further enhances and supports their biological efficacy in reducing thrombosis and inflammation [11,19].

It should also be stressed that similar anti-inflammatory and anti-thrombotic PLs bioactives rich in such bio-functional UFA (MUFA and PUFA) are also present in several other alcoholic beverages with health promoting properties associated with their moderate consumption, which are also produced by yeast-based fermentations, including wine and apple cider, as well as in their remaining by-products [10,75,76] and in yeasts utilized for producing such products, including the beer making brewing process [77,78]. This further supports the crucial role of yeasts and the fermentation process on the production and presence of PL bioactives rich in bio-functional UFA, with anti-inflammatory and antithrombotic health benefits.

Overall, various beer types, their constituents, and brewing by-products demonstrate anti-thrombotic and anti-inflammatory properties, attributed to the bioactive PLs they contain; even though they are present in traces in beer, these bioactive PLs act as potential agents providing health benefits against inflammation-linked chronic disorders [8,11,19,72]. Thus, moderate beer consumption (1-2 drinks/day) may potentially reduce platelet aggregation, HDL cholesterol, and fibrinogen levels, which are related with several CVD [2,8]. However, additional in vivo studies are needed to further substantiate the potential health benefits of beer bioactive PLs.

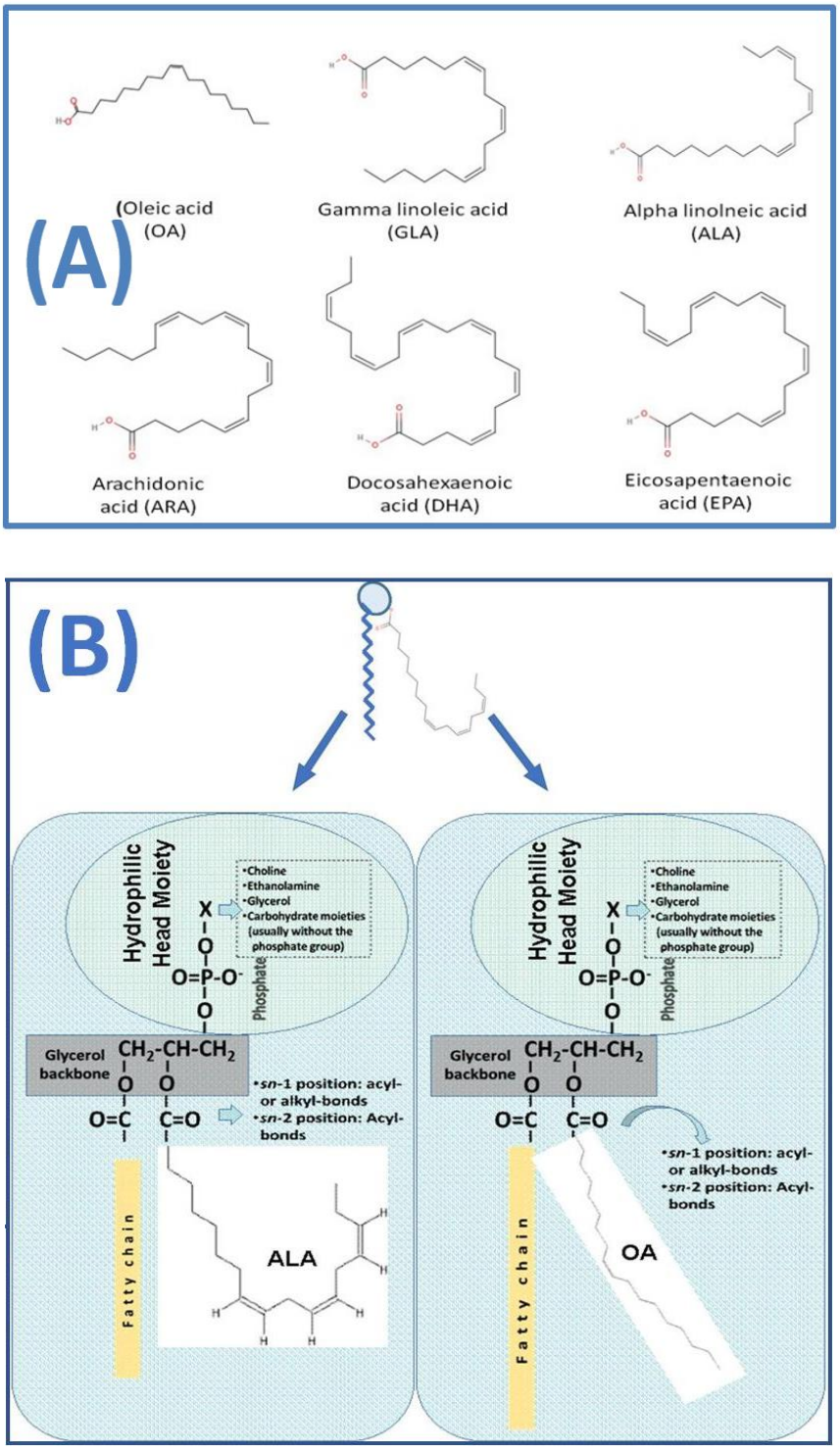

Figure 2. Lipid bioactives of beer and brewery by-products with anti-inflammatory and antithrombotic properties; (A) Bioactive UFA (obtained from https://molview.org/; assessed on 31st of December 2023), which can inhibit the ARA (also shown) derived pro-inflammatory signaling (B) Representative bioactive Polar Lipids bearing UFA at the *sn*-2 position of their glycerol (presented here) or sphingosine (not presented) backbones. (Abbreviations: UFA = unsaturated fatty acids; ALA = alpha-linolenic acid; OA: oleic acid; ARA: arachidonic acid).

3. Beer and brewery by-products bioactives in functional foods, supplements, and nutraceuticals

3.1. The role of beer bioactives in the observed health benefits associated with moderate beer intake

For decades there has been a global concern in regard to alcohol consumption in the form of several alcoholic beverages, including beer. A correlation among alcoholism and excessive beer intake has been discussed, while critics link beer consumption to heightened mortality rates and detrimental health effects [79,80]. On the contrary, there is an increasing interest regarding the potential health benefits linked to moderate beer consumption, attributed to the presence of beer bioactives [2,8]. The association of alcohol and health effects is versatile; it is well-known that light to moderate drinking is associated with reduced risks of conditions like all-cause mortality, diabetes, and heart diseases, while on the other hand, high amounts of beer consumption are correlated with a higher risk of death and the development of CVD. This complex correlation is often clarified by the J-shaped curve, which suggests that low to moderate alcohol intake is linked to lower arterial stiffness and reduced CVD-related mortality, while both non-drinkers and heavy drinkers face an increased risk of CVD and other disorders [2].

According to recent studies, fermented alcoholic beverages like wine, cider, and beer that are rich in bioactives have been characterised as functional foods-beverages with several antioxidant and anti-inflammatory health benefits (Figure 3). These functional bioactives and properties of beer are tightly linked with the health benefits associated with moderate beer consumption, such as the reduction of risk for various disorders, including cancer, CVD, and neurodegenerative disorders [8]. These health-promoting effects are attributed to the diversity of bioactives originating from malt and hops in beer, as well as in the yeast utilized in the fermentation, which may also explain why non-alcoholic beers have also demonstrated similar advantages. These non-alcoholic beers contain bioactives, namely hop-derived bitter acids, polyphenols, vitamins, and melanoidins, which offer health benefits even in the absence of alcohol [8,80,81].

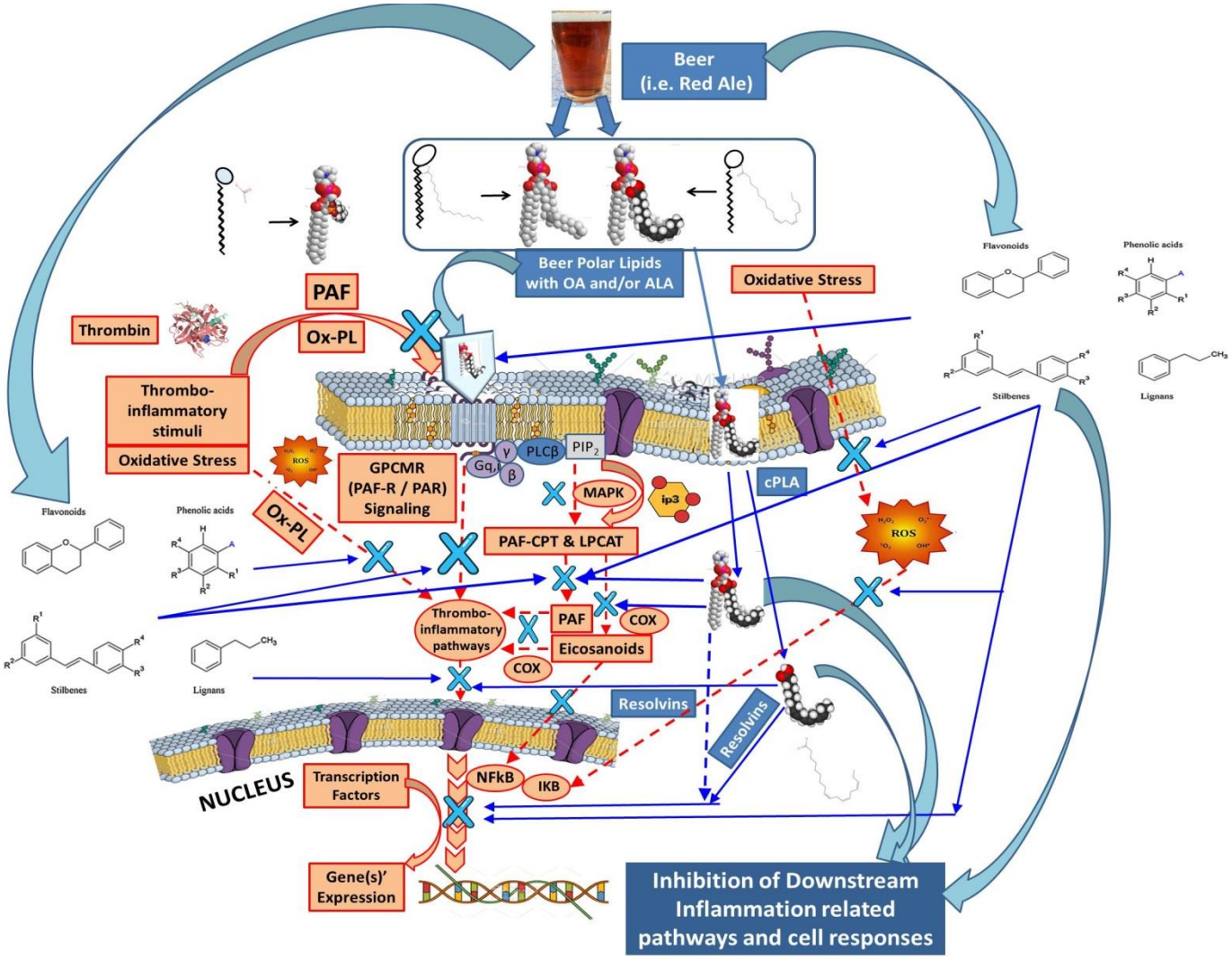

Figure 3. The mechanisms of action of the anti-inflammatory and antithromotic properties of beer PL bioactives and the antioxidant and anti-inflammatory capacity of beer phenolics.

Red Colors: Representative signaling of thrombo-inflammatory stimuli, such as those of PAF and thrombin, which after their binding in their GPCMR initiate cascades of further PAF synthesis by induction of PAF-basic biosynthetic enzymes, PAF-CPT, and LPCAT, as well as by COX activation that also produces several eicosanoids and prostaglandins, while all of these steps and inflammatory mediators facilitate through a vicious cycle the propagation of the thrombo-inflammatory signaling and the expression of inflammatory genes concluding in a downstream inflammatory activation and associated cell responses. Oxidative stress also induce these pathways, i.e. through the production of Ox-PL which imitates the pathogenic role of PAF on its receptor, and thus further induction of the inflammatory signaling, while the production of ROS can also facilitate the production of OX-PL and the expression of inflammatory genes, which further propagate the inflammatory cell responses. **Blue Colors:** Beer bioactives, such as Beer PL rich in UFA and several beer phenolics, affect beneficially all these signaling pathways, either through inhibition of PAF and Thromin binding on their receptors and/or through reduction of the thrombo-inflammatory signaling (after PL and phenolics being infused within the cell due to their amphiphilic nature and after the UFA are released

by cPLA2), which take place by modulating PAF metabolism and COX activities for reducing the levels of PAF, eicosanoids, and prostaglandins, and increasing the levels of Resolvins, and thus further inhibiting the expression of thromo-inflammatory genes and associated cell responses, and/or through scavenging and de-activating the ROS and the associated signaling cascades and trascription factors (the blue X represents an inhibitory effect on a pathway and/or an enzyme and/or a receptor and/or a transcription factor by beer bioactives as indicated by the blue arrows). Overall, beer phenolics and PL bioactives exhibit their anti-inflammatory and antioxidant health promoting properties by affecting all these pathways of thrombo-inflamation and oxidative stress, and thus the associated inflammatory manifestations and cell responses linked to several chronic disorders. Abbreviations: PAF = platelet-activating factor; GPCMR = G-protein coupled membrane receptors; PAF-R = PAF-receptor; PAR = Protease-activated receptors for thromin; PAF-CPT and LPCAT = the basic biosynthetic enzymes of the two dinstict pathways of PAF-synthesis, PAF-cholinephsphotransferase and lyso-phosphatidylcholine acetyltransferase 2, respectively; cPLA = cytoplasmic phospholipase A_2; MAPK = Mitogen-activated protein kinase; IP_3 = Inositol trisphosphate; OA = oleic acid; ALA = alpha-linolenic acid; UFA = unsaturated fatty acids; COX = cycloxigenase; NF-kB = Nuclear Factor kappa beta; IKB = inhibitor of. NF-kB; ROS = reactive oxygen species. (Cell/nucleus membranes depicted were reproduced from https://mindthegraph.com/; accessed 25/1/2024).

The impact of moderate beer consumption on health has been investigated through various means, including epidemiological studies, animal models, human trials, prospective cohort studies, and randomized controlled trials. These investigations aim to understand its effects on antioxidant capacity and its potential benefits against thrombosis, inflammation, and related conditions such as cardiovascular health (Table 1). Additionally, research has explored its role in enhancing gut microbiota, influencing serum biomarkers, and providing benefits in managing other chronic disorders (Table 2).

3.1.1. Moderate beer consumption and cardio-protective effects

An association among low to moderate consumption of fermented alcoholic beverages, namely beer, wine, and cider, to numerous health benefits has been reported by several studies; specifically, in terms of cardio-metabolic factors, namely coagulation, endothelial function, inflammation, lipid profiles, and protective effects against heart-related conditions have been demonstrated [2,8,10]. According to some studies, low beer consumption reduces the risk CVD and myocardial infarction; the ATTICA study in Greece revealed a 57% lower CVD risk in participants who consumed ≤ 1 glass of beer/week, with a dose-response relationship between ethanol intake and CVD risk [82]. A Swedish cohort study supported the protective effects of beer when consumed at 7–14 drinks/week against myocardial infarction and heart failure [83], while according to a large animal study, beer consumption reduced ventricular arrhythmia during severe ischemia, lowered oxidative stress, and protected the heart through the preservation of sirtuin-1, an essential antioxidant molecule [84]. The Norwegian HUNT study further suggested an inverse association between low to moderate alcohol intake, including beer, and the risk of heart failure [85]. Even though such studies showed that low to moderate beer consumption is associated with a reduced risk of heart failure and myocardial infarction, they did not investigate the specific mechanisms behind beer's cardio-protective effects; they only hold the perspective that these effects may arise from various factors and they suggest that light to moderate beer consumption could be associated with improved insulin sensitivity, increased serum HDL-C levels, and reduced levels of fibrinogen and platelet aggregation [82,84]. Endothelial injuries are also

associated with CVD risk by contributing to conditions like arterial thrombosis, atherosclerosis, and hypertension [7]; endothelial progenitor cells (EPCs) may be enhanced by polyphenols of beer [86,87], similar to the effects seen in red wine. This was demonstrated by randomized control trials involving high cardiovascular risk males, in which the impact of polyphenol-rich beverages (beer and non-alcoholic beer), on coronary heart disease (CHD) biomarkers was investigated in comparison to consuming gin [86,87]. Both non-alcoholic and alcoholic beer raised circulating EPC levels not observed with gin, attributed to polyphenolic content, not ethanol [86], and this effect may be due to polyphenols triggering SDF1-mediated mechanisms that enhance EPC mobilization or survival, potentially benefiting cardiovascular health through moderate beer consumption.

In a randomized trial involving premenopausal women, moderate beer consumption led to an increase in both total and high molecular weight (HMW) adiponectin levels, in contrast to non-alcoholic beer consumption and abstaining from beer; increased adiponectin levels are associated with improved insulin sensitivity and reduced inflammation, thereby reducing the risk of cardiovascular disease [88]. Additionally, moderate beer consumption has been associated with elevated levels of cardio metabolic markers, including adiponectin and HDL cholesterol that led to reduced risk of developing CVD due to the atheroprotective effects of HDL cholesterol [82,89,90]. Another prospective randomized crossover study indicated that both alcoholic and non-alcoholic beer inhibited LDL oxidation, increased the protective effects of HDL cholesterol against atherosclerosis, and facilitated the removal of cholesterol from macrophages. Notably, no detrimental effects on weight or overall health were observed with light to moderate beer consumption [27,91], while according to another study, drinking beer resulted in a significant decrease in glucose, insulin, and fasting insulin resistance levels, suggesting better glucose regulation and increased insulin sensitivity, which may prevent conditions like dyslipidemia, hypertension, type 2 diabetes, and CVD [80].

Beer and red wine also prevented hyperoxia-induced arterial stiffness increase, with beer's purine content boosting plasma uric acid and antioxidant capacity [92], while, additionally, another human study showed that low beer consumption acutely reduces arterial stiffness for an hour, possibly through structural or functional changes [93]. The influence of moderate beer consumption on cardiovascular risk factors, such as aortic pressure and stiffness, endothelial function, and pressure wave reflections, was investigated in a single-blinded trial, and moderate beer intake led to improved arterial markers and to a positive impact on pulse pressure amplification, maybe associated with reduced aortic stiffness and pressure wave reflections, which may reduce atherosclerosis, lowering CVD morbidity and mortality [94]. Even though the exact mechanisms remain unclear, it is hypothesized that beer's bioactives may collaborate with alcohol to cause these health benefits.

As for the immune system's response to mental stress, beer consumption beneficially affected it, according to a randomized crossover study, in which alcoholic beer consumption led to a significant decrease in cortisol levels and adrenocorticotropic hormone and a lower response of IL-8, a molecule strongly associated with atherosclerosis, after drinking beer vs non-alcoholic beer, following the mental stressor, suggesting potential atheroprotective effects of beer during stressful situations [95]. Moderate beer consumption is linked to lower levels of plasma fibrinogen, a marker strongly linked to elevated cardiovascular risk and higher concentrations of serum uric acid that may contribute in preventing cardiovascular diseases. A prospective cohort study also suggested that alcohol, including beer, could affects circulating cholesterol fatty acids, as it was associated with elevated levels of specific fatty acids, namely arachidonic, eicosapentaenoic, γ-linoleic, myristic, and palmitic acids [96], which also are key factors in health and chronic diseases [97]. The above findings suggest a potential

cardiovascular benefit linked to moderate beer consumption, although further research is needed for a comprehensive understanding of these effects.

Table 1. Cardio-protective health effects of moderate beer consumption.

Study design	Observed result(s) & Health-promoting effect(s)	Benefits observed—Mechanisms of action(s)	Ref.
Different commercial beer samples (22) were assessed in a combination of in vitro and in vivo animal trials (Male Wistar rats).	a) A vasorelaxant effect associated with beer consumption. b) A correlation with the antioxidant properties of the assessed beer samples. c) A vasorelaxant effect associated with beer consumption.	↓ in the formation of thiobarbituric acid-reacting substances.	[51]
A prospective population-based study in a cohort of 2.583 individuals who completed a 10-year follow-up, with complete information available for 2.020 participants, equal males and females.	A lower consumption of ethanol was associated with a reduced incidence of CVD.	Individuals who drank ≤1 glass of beer/week exhibited a notably diminished risk of developing CVD.	[82]
A prospective Swedish cohort study in 33,760 male participants, aged 45–79 years. Participants completed a 96-item food frequency questionnaire.	Alcohol consumption was associated with a reduced risk of myocardial infarction, which is a known risk factor for heart failure.	U-shaped relationship between the incidence of heart failure and alcohol consumption.	[83]
An animal study in 30 4-month-old female swine.	Favorable ventricular healing process and a smaller scar size.	Consuming beer was linked to ↓ in the occurrence of ventricular arrhythmia.	[84]
A randomized crossover clinical control feeding trial in a cohort of 33 high-risk males aged between 55–75 years. Six sequences of interventions were included, each lasting for 4 weeks.	Beer polyphenols played a role in reducing biomarkers of inflammation and the quantity of leukocyte adhesion molecules.	a) Beer polyphenols were associated with ↓ blood pressure and ↓ homocysteine levels. b) Improvements in HDL cholesterol, ApoA-I, ApoA-II, and ↓ serum fibrinogen.	[87]
A randomized, single-blinded, crossover study in 17 male participants with an average age of 28.5 ± 5.2 years.	The consumption of beer → improved endothelial function when compared to the other test drinks.	The consumption of beer demonstrated + impacts on pulse pressure amplification, influenced by ↓ aortic stiffness.	[94]
A randomized, open-label, crossover controlled clinical trial in 36 high-risk men aged 55–75.	Both non-alcoholic and alcoholic beer consumption were + associated with ↓ circulating EPCs.	The observed effects on EPCs were due to mobilization or enhanced survival, mediated by the SDF1 mechanism.	[86]
A randomized crossover study in 10 healthy male participants aged 21–29 years. A control group was also included for reference.	Beer, along with wine and vodka, successfully hindered the rise in arterial stiffness triggered by hyperoxia.	The high purine content in beer was associated with an elevation in plasma uric acid levels.	[72]

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Study design	Observed result(s) & Health-promoting effect(s)	Benefits observed—Mechanisms of action(s)	Ref.
A population-based cohort study in 60.665 Norwegian men and women, aged ≥20 years. A CAGE questionnaire was also employed to identify potential problem drinking behavior.	Low to moderate alcohol consumption was inversely linked to the risk of heart failure.	A hazard ratio of 0.87 was identified for heart failure in association with beer consumption.	[85]
A prospective open study utilized a randomized two-arm, longitudinal crossover design in 36 overweight men and women, aged 40–60 years old.	Moderate and regular beer intake can enhance HDL-induced cholesterol efflux, which is beneficial for cardiovascular health.	No substantial alterations were noted in body weight or waist circumference after both intervention periods, and no adverse effects were observed.	[91]
An observational cross-sectional study in 240 Spanish men and women, aged 55–85 years.	Moderate alcohol intake, encompassing wine and beer consumption, was linked to ↑ levels of HDL-C and adiponectin.	Beer intake was associated with higher mean platelet volume (MPV), which is recognized as an emerging biomarker for CVD.	[89]
A single-blinded study in a cohort of 11 male participants with an average age of 21.1 ± 0.2 years.	A ↓ in arterial stiffness observed, due to the alcohol content within the beer.	a) No notable distinction in ↓ of arterial stiffness between non-alcoholic beer and regular beer. b) The consumption of 200 and 350 mL of beer induced a temporary ↓ in arterial stiffness that endured for 60 min.	[93]
A study in 15 men aged 20–57 years old. Three 30-day periods were employed.	Alcoholic beer consumption had a favorable influence on most lipids, resulting in ↓ levels of LDL and ↑ levels of HDL compared to non-alcoholic beer.	Alcoholic beer consumption induced negative effects on oxidative balance, primarily attributed to the alcohol content.	[80]

3.1.2. Other health benefits associated with moderate consumption of beer

Various other health benefits have been linked with moderate beer consumption, such as gut microbiota composition and neurodegenerative diseases. Moderate consumption of fermented beverages like beer can potentially reduce the likelihood of neurological disorders [98], while they also may prevent dementia and Alzheimer's disease through various mechanisms, namely antioxidant activities, increased serum HDL, and vasodilation, as suggested by a 3-year prospective study which found lower dementia risk in moderate alcohol consumers [98]. Another prospective study in Helsinki showed that beer consumption led to a negative link with amyloid Beta induced immunoreactivity, implying potential defence against amyloid Beta aggregation and reduced Alzheimer's risk [98], while a prospective cohort study suggested that consuming low beer quantities was associated with reduced risk of Parkinson's compared to higher-risk spirits [99]; such results were supported by *in vitro* studies too, and found that extracts from dark beer, lager, and non-alcoholic beer had neuroprotective effects through several mechanisms, maybe attributed to their high phenolic content [100]. Beer and its bioactives positively affect the composition and diversity of gut microbiota [101–103], according to a study comparing alcoholic and non-alcoholic beer. Alcoholic beer increased bacteroidetes and decreased firmicutes, while non-alcoholic beer increased the beneficial bacteria *Streptococcu*s and

Veillonella, which have immunomodulatory properties [101]. Lacking alcohol, the polyphenols of the non-alcoholic beer enhanced gut microbiota diversity, potentially resulting in antioxidant and anti-inflammatory effects, benefiting glucose tolerance, and preventing disorders, namely hypertension and diabetes [101,103], while a positive impact of different phenolic content beers on the composition of gut microbiota was observed [102]. These promising findings further suggest that more studies are needed in order to fully understand the beneficial impact of low/non-alcohol functional beers fortified with antioxidants, probiotics, and dietary fibre on gut-microbiota.

Table 2. Moderate beer consumption and health promoting properties on serum biomarkers and other chronic disorders.

Study design	Observed result(s) & Health-promoting effect(s)	Benefits observed—Mechanisms of action(s)	Ref.
A comprehensive analysis with both in vitro and in silico assessments, involving the scrutiny of 11 commercially available beer samples	Polyphenols interact on serum proteins, thereby enhancing their binding capacity and antioxidant properties	Flavonoids played a significant role in bolstering the beneficial characteristics of beer.	[44]
An *in vitro* study to investigate the neuroprotective and antioxidative effects of beer and to evaluate its influence on the expression of adenosine receptors in neurodegeneration cellular models.	Beer effectively modulates the expression of adenosine receptors, offering protection to glioma and neuroblastoma cells from oxidative stress.	Beer's antioxidant ability to reduce cell death triggered by hydrogen peroxide and linked the beer's protective properties to an enhancement in A1AR activity.	[100]
A prospective 3-Year Follow-Up study among 3.202 Primary Care Attendees Aged ≥70 years, to investigate the connection between alcohol consumption & Alzheimer's dementia.	Association between alcohol consumption and dementia might not be causal.	Individuals who consumed alcohol lightly to moderately had a significantly ↓ risk of developing dementia.	[71]
A Prospective cohort Study in 306.895 US participants, aged 50–71 years old, to investigate the potential association between alcohol consumption and Parkinson's Disease.	Beer consumption was linked to ↓ risk of developing Parkinson's Disease.	The ↑ purine content in beer, with ethanol, contributed to the augmentation of plasma urate levels.	[99]
A prospective cohort study in 125 males, aged 35–70 years, to evaluate the relationship of alcohol consumption with Alzheimer's disease and the aggregation of β-amyloid in the brain.	Beer consumption may be a protective factor against β-amyloid aggregation in the brain, potentially reducing the risk of Alzheimer's disease.	There was a - association observed between the consumption of beer and the presence of β-amyloid immunoreactivity.	[29]
A prospective cross-sectional cohort study in 3.975 participants (both men and women) aged 60 years, to examine the association between alcohol consumption and serum fatty acids.	Individuals who consumed beer had the ↓ concentration of plasma fibrinogen and the ↑ concentration of serum uric acid.	Alcohol-intake correlated with ↑ levels of fatty acids and ↓ levels of saturated pentadecanoic acid and n-6 polyunsaturated linoleic acid.	[96]
A randomized, double-blinded, placebo-controlled prevention trial spanning 8 years, in the 13-Year Follow-Up SU.VI.MAX 2 Cohort of 3.088 participants aged 45–60, encompassing both to investigate the potential influence of alcohol consumption on cognitive performance.	Intake of >10% ethanol in men was associated with ↓ cognitive performance. In women moderate alcohol intake → a favorable association with cognitive performance.	Men who had a ↑ contribution of beer to their overall alcohol intake tended to exhibit lower cognitive scores.	[104]

Continued on the next page

Study design	Observed result(s) & Health-promoting effect(s)	Benefits observed—Mechanisms of action(s)	Ref.
A randomized, open-label, crossover trial in 24 male participants aged 21–40 years, to evaluate the effects of whole beer consumption on the physiological stress response.	Moderate alcohol consumption may protect against responses of stressful events, as it expedited the decline in plasma cortisol and ACTH levels and reduced the reaction of inflammatory cytokines.	ACTH and plasma cortisol levels experienced ↓ following the consumption of regular beer in contrast to non-alcoholic beer.	[95]
A randomized open-label crossover study in 24 premenopausal women, 20–40 years, to evaluate the effects of consuming whole beer on adiponectin levels.	↑ in the concentration of both total and HMW adiponectin was observed after a 3-week period of consuming beer.	No significant impact on serum triglyceride levels due to alcohol consumption.	[88]
A bi-annual follow-up cohort study spanned over a period of 19–28 years in 360 participants with early-onset Alzheimer's Disease of cohorts, to evaluate the association of alcohol consumption, with cognitive decline and the progression of Alzheimer's disease.	Significant benefits associated with low-to-moderate alcohol consumption concerning Alzheimer's disease, were not observed.	Heavy alcohol consumption, particularly of hard liquor, was linked to a faster rate of cognitive decline among individuals with early-onset Alzheimer's disease.	[105]
An animal study (N = 18) in 5xFAD transgenic mice, versus non-transgenic wild-type mice (control group). Furthermore, 12-month-old J20 mice were incorporated into the research.	Iso-α-acids inhibit inflammatory reactions, ward off inflammation, alleviate cognitive deterioration, and diminish excessive neural activity in the hippocampus within mouse models. b) Consumption of 1 L of beer/day can supply a sufficient dose of iso-α-acids, potentially improving memory impairment, even in individuals already affected by Alzheimer's disease.	Iso-α-acids: a) inhibit inflammatory cytokines & chemokines → amelioration of hippocampal inflammation and neural activity, b) activate peroxisome proliferator-activated receptor-γ, c) reduced the levels of soluble Aβ1-42 in the hippocampus, which is associated with increased inflammation, d) augment the expression of CD36, a factor involved in the phagocytosis of amyloid-β in the brain.	[106,107]
A cohort study in 70 Mexicans, aged 21–55, to investigate the influence of moderate beer consumption on human gut microbiota and its subsequent effects on fasting glucose levels and beta-cell function.	The presence of alcohol in beer had an impact on the improvement of gut microbiota. b) Moderate consumption of both alcoholic and non-alcoholic beer did not result in ↑ risk of cardiometabolic issues.	a) Alcoholic beer led to ↑ in fasting glucose levels and ↓ in the percentage of functional β-cells as compared to non-alcoholic beer consumption, b) changes in gut microbiota: ↓ in *Firmicutes* and ↑ in *Bacteroidetes* and *Proteobacteria* following alcoholic beer consumption.	[101]
A Randomized Crossover Trial in 20 subjects (10 healthy volunteers and 10 individuals with metabolic syndrome), to evaluate the effect of three different phenolic-content beers on the gut microbiome and the potential role of the induced shifts in the antioxidant capacity of beer polyphenols.	The antioxidant capacity of beer polyphenols may induce + shifts in gut microbiota composition, and the observed changes may also boost the antioxidant capacity of these compounds.	a) Some of the detected differences appeared to be related to the metabolic status, b) ↓ in porphyrin metabolism & heme-biosynthesis was found after beer consumption.	[102]

3.1.3. Detrimental effects of beer intake abuse

Several studies have associated beer consumption to various health issues, including cancer, cognitive decline, cerebrovascular disease, ischemic heart disease, cardiovascular events, and all-cause mortality [20,21,79,104,105,107–109]. Nevertheless, in several studies subjects chosen to be studied as a comparison group belong sometimes to unhealthy non-drinkers, which may bring discrepancies to the outcomes, while when assessing cardiovascular benefits, some studies focus only on ischemic heart disease, not accounting for overall cardiovascular risk; lumping all alcohol types together in research can underestimate the risks associated with specific beverages, too.

Mostly epidemiological studies have associated high alcoholic beer consumption with the risk of various cancer types, namely breast, colorectal, esophagus, larynx, and liver cancer [79,109]. Even though the exact mechanisms responsible for these cancers remain unclear, it is suggested that the increasing alcohol intake could be a significant factor, since ethanol metabolites, such as acetaldehyde, are carcinogenic and may lead to the development of cancer by disrupting DNA replication, forming DNA adducts or causing DNA damage. Additionally, ethanol may contribute to folate deficiency or immunosuppression, which could promote the spread of tumors. In light of these discoveries, there is a growing interest in developing alcohol-free beers that can preserve the positive health aspects while minimizing the negative effects attributed to alcohol [104,105,107,108].

3.2. Valorisation of brewery by-products' bioactives as bio-functional ingredients in health-promoting functional foods

There is a growth of interest in isolating valuable constituents from brewing by-products to develop novel functional food products, with various extraction methods employed for this purpose, including novel and emerging approaches and environmentally friendly (green) technologies [69]. BSG, BSH, and BSY are the most important brewery by-products, each of which contain a range of bioactives that can be valorized for the production of health-promoting novel products.

BSG has been valorized in a great range of uses, including livestock feed, flavor precursors, a medium for microbial and enzymatic growth, and a raw material for the production of bioethanol. Additionally, BSG polyphenols (i.e. ferulic, p-coumaric, p-hydroxybenzoic, syringic and vanillic acids), protein hydrolysates, and fiber have been studied for their potential health benefits and applications as ingredients in several products. For example, fortification of muffins with brewer's spent grain protein hydrolysates enhanced their *in vitro* antioxidant and antidiabetic (α-glucosidase and α-amylase inhibitory) bioactivities, while oxidative stability, hardness, color, and sensory properties of the fortified muffins achieved similar overall acceptance as the control [110]. Moreover, BSG dietary fiber, such as hemicellulose components (i.e., arabinoxylan), possess prebiotic bio-functionalities in the large intestine, while BSG β-glucans can reduce CVD-risk by decreasing cholesterol levels through increasing gastrointestinal viscosity and cholesterol-derived bile acid production [32,111]. Subsequently, consuming BSG bread could supply the Recommended Dietary Allowance (RDA) of dietary fiber from BSG, while several antioxidant and anti-inflammatory benefits were enhanced in the novel products with marketable health claims [30,112]. BSG has also been used as a functional ingredient in several other bakery products, such as extruded snacks, in which it significantly boosted their fiber content, and it increased protein content by 50%, essential amino acids by 10%, and reduced calories by 7% as compared to wheat flour bread [22].

Utilizing BSG in high-fiber, low-fat meat products may minimize synthetic antioxidants, while enhancing foods health-promoting properties. Additionally, BSG may be used as a partial replacement for animal protein in sausages and other meat products [22]. BSG has also been used to enhance dietary fiber and protein content in pasta without affecting the pasta's structure [113]. Among BSG vitamins, tocochromanols (a type of vitamin E) are a primary focus in some BSG studies. Tocochromanols are lipophilic antioxidants produced by plant organisms and are known to reduce LDL cholesterol levels, potentially serving as anticancer and neuroprotective agents; additionally, BSG contains high mineral content, featuring significant levels of calcium (3600 mg/kg), magnesium (1900 mg/kg), phosphorus (2900–6000 mg/kg), and potassium, and also contains copper, iron, manganese, and sodium in traces [32,65].

Apart from the traditional uses of BSH as fertilizer or as an enhancer of yeast activity when being re-incorporated into the brewing process leading to increased beer production yields, BSH phenolics have been extensively investigated as ingredient(s) to produce fortified foods and other functional products, supplements and nutraceuticals with potential health benefits. For example, pasta fortified with trub, up to 10%, reduced glucose release without compromising sensory characteristics or product quality [114].

BSY is commonly used as a carbon and nitrogen source for microbial cultivation during various food processing steps, as well as in the production of health-promoting foods, while the excess of BSY is a valuable sustainable source of several constituents with nutritional value and health promoting properties [69]. For example, BSY extracts have shown significant anti-obesity properties, since excess yeast extract reduced cell apoptosis and lower the survival rates of preadipocytes (precursors to fat cells) and adipocytes (fat cells). In animal studies, administering brewer's yeast biomass with ethanol to male Sprague-Dawley rats reduced perirenal fat and levels of triglycerides in serum and liver and enhanced the liver’s antioxidant capacity.

Extracts derived from BSY have also demonstrated significant anti-tumor effects by increasing the expression of proteins from the mitogen-activated protein kinase (MAPK) family, including p-ERK1/2, p-JNK, and p-p38, but also by suppressing at the same time the production and levels of cyclin D1 and cyclin E1, resulting in G0/G1 cell cycle arrest in both A549 cancer cells and in H460 lung cancer cells, with xanthohumol and hop bitter acids being the key factors in these two studies [69].

Moreover, BSY’s hydrocolloid fibers, namely β-glucan, offers versatility in the food industry since it can be used as an emulsifier, thickener, water and oil retainer, and foam stabilizer, utilizing surplus yeast resources, while BSY β-glucans find applications in medicine, due to their immune-enhancing properties. Branched β-1,3-glucans have been found to stimulate the immune system compared to their linear counterparts. Insoluble β-glucans have gained attention for their usefulness as polysaccharides with diverse health benefits, while their contribution to infection prevention, immunity, and seamless integration into medicinal contexts underscore their value [115].

The bioactive characteristics of β-glucans, namely antioxidant, blood-lipid regulation and prebiotic effects make them be appealing components for enhancing functional meals. Successful incorporation of various β-glucan fractions into food products, including breakfast oats, pasta, noodles and dairy items has been demonstrated [116]. Additionally, whole grains consumption, containing β-glucans, has been associated with a reduced risk of coronary heart disease, with β-glucan being a key nutritional constituent; β-glucan’s soluble nature and its ability to form gel-like structures, increasing gastrointestinal viscosity, which is thought to hinder the reabsorption of bile acids and promoting their production from cholesterol, results in an overall reduction in cholesterol levels. To achieve a cholesterol-lowering effect, a daily intake of at least 3 g of barley β-glucan is required [32].

Yeast β-glucans are present in a variety of food products, namely biscuits, cereals, cereal bars, chocolates, crackers, dietary supplements, fruit juices, protein bars, soups, yogurts, and so on, while the incorporation of β-glucan into these foods enhance functional properties, transforming them into functional foods [38]. Specifically, zymosan, an insoluble form of β-glucans and glucose polymer with antibacterial properties found in *Saccharomyces cerevisiae*, enhanced the immune system by activating macrophages and stimulating the secretion of cytokines. Additionally, zymozan exhibits antioxidant effects and promotes the release of tumor necrosis factor (TNF-α). β-glucans may enhance immunity when present in sufficient quantities by assisting skin cells in neutralizing free radicals, providing protection against environmental pollutants and cellular aging [38].

Several peptides present in BSY, with both hydrophilic and hydrophobic characteristics and antioxidant and antihypertensive effects, are also suitable ingredients in food and animal feed [117]. BSY contains vitamin D and relevant gene encoding for its production, and thus BSY also represents an economical source for enhancing ergosterol with D2 (ergocalciferol) derived from the precursor ergosterol. Vitamin D2 produced from yeast sources is used as a dietary supplement, since, other than its crucial role in the musculoskeletal system, vitamin D has been also associated with various health benefits like anti-inflammatory properties. Vitamin D and its analogs can significantly reduce platelet aggregation induced by thrombotic and inflammatory mediators such as platelet-activating factor (PAF) and thrombin [118]. Administration of paricalcitol, a vitamin D analogue, for a month in patients undergoing hemodialysis led to reduced PAF levels by inhibiting its production, resulting in reduced inflammation and lower levels of other significant inflammatory cytokines, including TNFa and IL-6 [118]. Vitamin D can reduce levels and/or inhibit thrombo-inflammatory mediators, and thus it appears to be a key factor in the mitigation of the risk of chronic illnesses [6,7]. BSY is also a valuable source for the large-scale production of nucleotides as it contains approx. 10% nucleic acids. Such nucleotides serve as aroma and flavor enhancers in several food products, including soups and grains, since they are used in small quantities and they may replace common flavor enhancers of animal origin [23].

4. Beer and brewery by-products' bioactives in cosmetics, cosmeceuticals, and pharmaceuticals

In recent years, there has been increasing interest in the application of the by-products from the food and beverage industry, such as BSG, BSH, and BSY, in the biotechnological and pharmaceutical industries due to their distinct characteristics and composition [34], while at the same time consumers have been increasingly demanding whole and natural ingredients for formulating in these sectors. Thus, cosmetic manufacturers are investigating alternatives to synthetic and non-sustainable components [119]. However, studies regarding the fortification of cosmetics and drugs with bioactives from beer and brewery by-products are scarce and have only been quite recently reported.

According to the literature, BSG, due to its content in valuable bioactive microconstituents such as phenolic compounds, has undergone several different extraction processes for its potential revalorization. Even though high-polyphenolic BSG extracts have been thoroughly evaluated as potential nutraceutical ingredients, their implementation in the cosmetic industry has only recently started to be the aim of scientific studies [119–121]. For this purpose, several low-cost and simple extraction methods have been applied for bioactive polyphenol recovery from BSGs, such as solid/liquid-based extractions and Soxhlet extraction [122], while environmentally friendly approaches, such as the use of "green" solvents and techniques, have been also proposed in accordance

with international regulatory standards [123,124]. BSG phenolics were found to exhibit *in vivo* antioxidant and skin-lightening properties after their addition in cosmetics [119], while according to the same study, the main component of BSG, that is hemicellulose, can also be incorporated into the formulations of cosmetic products as an amphiphilic stabilizer. It is worth noting that such an implementation represents a rather promising example of amphiphilic hemicellulose-based fatty micelles synthesis with potential uses in drug delivery, food, and cosmetic industries due to long-lasting stability [119]. Additionally, polyphenolic-rich extracts from BSG have been found to inhibit the tyrosinase activity of in vitro keratinocyte cultures with low cytotoxicity [60,119,125].

A BSG derived extract has also shown antioxidant and antimelanin synthesis (antimelanogenesis) effects, as they showed high DPPH radical-scavenging activity and inhibited α-MSH-induced melanin synthesis and reduced the expression levels of MITF, TRP-1, TRP-2, and tyrosinase by regulating the MAPK pathway in B16F10 cells cultured in both 2D and 3D environments, as well as in 3D reconstituted human skin and zebrafish embryo models, with ferulic acid and p-coumaric acid being identified by HPLC as the main phenolic bioactives to have whitening effects [126]. Thus, BSG derived extracts can be used in multifunctional cosmetics as a sustainable ingredient with antioxidant and skin-whitening properties.

Such results suggest that polyphenolic-rich BSG extracts may be applied as skin-lightening agents for cosmeceutical products, while even though there are several studies which have demonstrated the antioxidant activities of BSG polyphenolic extracts *in vitro*, *in vivo* testing and randomized clinical trials also remain a challenge due to the uncertainty emerging from the degradation, oxidation, and instability of the extracted BSG polyphenols. Furthermore, it is crucial that factors such as safety and reproducibility of the aforementioned results are examined thoroughly via *in vivo* model tests.

Apart from BSG and BSY derived phenolic compounds, and with respect to cosmeceutical- and drug-related applications of the bioactives derived from these by-products, it is also worth indicating that bioactive peptides from brewing by-products (spent grain and yeast) have shown antihypertensive properties, while peptides derived from the brewing industry maintain or present higher antihypertensive activity after simulation of oral administration, validating the usefulness of these peptides to reduce the risk, ameliorate, or treat primary hypertension, and thus enhance their potential to be used as supplements or nutraceuticals as well as anti-hypertensive drug alternatives of Angiotensin-converting enzyme (ACE) inhibitory drugs for blood pressure and hypertansion management [127]. Moreover, BSG protein hydrolysates rich in bioactive peptides, regulate the immune response, involving TLR2 and TLR4 and the activation of NFκB and MAPKs, an effect partly maintained after in vitro gastrointestinal digestion [128]. More specifically, BSG protein hydrolysates were found to induce production of the anti-inflammatory interleukin 10 and inhibition of the production for both tumor necrosis factor and interferon-γ in inflammatory stimulated (by lipopolysaccharide or concanavalin A) primary cultures of rat spleen cells, with splenic macrophages and T lymphocytes behaving in a similar fashion, while in spleen cells from TLR2−/− and TLR4−/− mice, immune-regulatory effects were greatly reduced or abrogated. The study of signal transduction pathways indicated a major involvement of NFκB, and the contribution of MAPKs p38, c-Jun N-terminal kinase, and extracellular signal-regulated kinases 1 and 2.

Moreover, bioactive peptides can be found in protein-rich extracts produced from BSY too, and several studies have described their positive impact on the human body, including antihypertensive, antioxidant, and antimicrobial effects, although other bioactivities have also been described, including antidiabetic properties, tumor cells proliferation inhibition, gastric mucosa protection, and anti-aging

and skin-health protection (wound healing stimulation and increase of collagen synthesis and skin elasticity), with the latter introducing a growing interest in cosmetic sectors for such BSY-derived peptide-/protein-rich cosmeceutical products [129]. For example, bioactive peptides from spent yeast waste streams, a byproduct obtained from the fermentation process, are of particular interest for skin care formulations and cosmetics as they have been shown to be safe and hypoallergenic while simultaneously being able to exert various effects upon the epidermis modulating immune response and a positive effect upon the production of skin metabolites relevant for skin health, such as collagen, hyaluronic acid, fibronectin, elastin, cytokeratins, and aquaporins [130]. The recovery of bioactive peptides from such brewery by-products for production of functional ingredients is an important step in the increasing demand to implement and promote a circular economy-based industry.

BSG derived fibers have also been linked to pharmacological benefits. For example, BSG rich in arabinoxylans (BSG-AX) has also been studied as an excipient release modifier for the release of drugs, by determining the release profile of drugs like metformin hydrochloride (MH) in water mediums, suggesting that such compounds from brewery spent grain by-products constitute suitable materials for producing prolonged drug release vehicles [131]. Glucans derived from spent yeast have also been proposed as a sustainable and safe ingredient for cosmetic and skincare formulations, as shown by a broad safety assessment in which no cytotoxic effect, immunomodulatory capacity (IL-6 and IL-8 regulation), genotoxicity, skin sensitization, and impact on the skin microbiota were observed [132]. Moreover, cellulose nanocrystal can be extracted from BSG and used as a stabilizer for Pickering emulsions, which find interesting applications in in the food, cosmetic, and pharmaceutical industries [133].

In addition, spent grain wax was used as one of the functional ingredients of an adsorbent lotion, which also contained tapioca starch, butyrospermum parkii extract, argania spinosa kernel oil, aloe barbadensis, rosehip oil, and allantoin, evaluated for the safety and efficacy for the treatment of mild-to-moderate intertrigo, a common inflammatory skin condition that is caused by skin-to-skin friction (rubbing) that is intensified by heat and moisture, through a randomized, double-blinded study in comparison to a 1% hydrocortisone cream [134]. More specifically, the anti-inflammatory efficacies of twice daily applied adsorbent lotion after two weeks of this treatment in 20 interrigo patients was equivalent to the application in another 20 patients of a low-potency steroid (1% hydrocortisone) cream, while the lotion was safe and produced excellent pruritus reduction, with high satisfaction of patients.

As for the bioactives that have been elicited from hops and hop-derived by-products, such as BSH, quite recent studies have proven anti-aging effects of such products from handcrafted beers in human keratinocyte cells, suggesting that they may be potent natural ingredients for the preparation of cosmetics. As already mentioned in the present review, hops and hop-derived by-products are sources of microconstituents with potential anti-inflammatory, antimicrobial, and antioxidant properties [135]; they may represent promising agents during their application in antiacne, anti-aging, deodorant, and skin-whitening cosmetic formulations [135]. In this context, a gel formulation with 0.3% hops extract, with standard humulone and lupulone concentrations, with antibacterial activity against *Propionibacterium acnes* and *Staphylococcus aureus*, both involved in inflammation and acne formation, was developed by Weber et al. (2019) [136].

As previously mentioned, BSH contains various bioactives, such as desmethylxanthohumol. The synergistic combination of these compounds suggests that BSH could serve as an exceptional plant-derived supplement. Additionally, BSH are sources of prenylated chalcones and flavonoids, both of which have shown promising results during preclinical studies for cancer treatment and prevention [137] due to their ability to regulate carcinogen metabolism by blocking phase 1 metabolic enzymes while

activating phase 2 detoxification enzymes [27]. Furthermore, it has been reported that bitter acids exhibit antifungal activity against *Candida albicans*, *Trichophyton*, and *Mucor* species, while they also displayed antibacterial activity against gram-positive bacteria, including certain species of *Micrococcus*, *Mycobacterium*, and *Streptomycetes* [27,138]. Recently, non-genotoxic, non-haemolytic organometallic silver spherical nanoparticles synthesized using an extract of spent hops intended for biomedical applications have demonstrated lower levels of cytotoxicity and genotoxicity towards normal cells [139]. Additionally, they exhibit excellent hemocompatibility, meeting important criteria for drug selection [139]. It is worth noting that the nanoparticles showed lethality effects towards both *E. coli* and *S. aureus* [139].

Furthermore, the *in vitro*, *ex vivo*, and *in vivo* benefits of major prenylated components in hops and spent hops in several human diseases including cancer, inflammation, and viral infections have extensively been reviewed, along with in silico studies of these prenylated bioactive compounds against various drug targets, such as histone deactylases (HDACs), sirtuins (SIRTs), and acetylcholinesterase (AChE), and the molecular molecular interactions between proteins and ligands and structure-activity relationship (SAR) studies [140]. In addition, several hops-derived chalcones have undergone investigation as potential drugs for lung cancers [141]. Chalcones exhibit anticancer activities, induce cell apoptosis, disrupt angiogenesis, and inhibit tubulin assembly. In pharmacological perturbation studies based on protein-level signatures, which are fundamental for drug discovery, by utilizing mass spectrometry (MS)-based proteomic platforms to profile the whole proteome of cells involved in several pathologies, such as the breast cancer MCF7 cell line under stress, revealed functional relevance in exploring the novel anti-tumor pharmacological activity of xanthohumol, as its proteomic pattern was similar to that of classic tubulin inhibitors, suggesting that xanthohumol shows antitumor effects by inhibiting tubulin assembly, which was also shown by *in vitro* immunofluorescence assays in cancer cells treated with xanthohumol [142].

Especially for xanthohumol, this hops-derived bioactive phenolic has also exhibited antitumor pharmacological effects, as well as antioxidant protection against several of the manifestations induced by other disorders, such as diabetes mellitus. For example, xanthohumol has been found to alleviate oxidative damage as it has attenuated hydrogen peroxide (H_2O_2)-induced cytotoxicity, ROS production, cell apoptosis, as well as high glucose-induced cell damage, but also via increase of expression, activation, and nuclear translocation of the nuclear factor erythroid 2-related factor 2 (Nrf2) trancription factor, with several health benefits including antidiaetic properties and beneficial effects against diabetes induced manifestations such as the diabetic skin ulcer by accelerating diabetic wound healing [143].

Overall the prenylated phytochemicals from *H. lupulus L.*, including xanthohumol, isoxanthohumol, 8-prenylnaringenin, and 6-prenylnaringenin, have shown promising roles in human health and may contribute to new drug discovery and development. Based on the above, several researchers have suggested xanthohumol as a promising lead compound and a potential food and/or drug candidate for the treatment of several pathologies, including diabetic skin ulcers. However, more *in vivo* studies are needed to validate the beneficial antioxidant, anti-inflammatory, and antitumor health promoting properties of these bioactives for io-functional foods, cosmetics, and drugs [140,141,143,144]. It is noteworthy that xanthohumol pharmacokinetics in all trials conducted based on xanthohumol administration/supplementation, especially at doses indicated by the European Scientific Cooperative on Phythoterapy (ESCOP), led to no adverse effects, suggesting that xanthohumol is safe and well tolerated with all clinical biomarkers and anthropometrics being unaffected and/or staying within the clinically normal reference range [46,145].

Nevertheless, even though numerous *in vitro* and *in vivo* experiments have demonstrated the selective anticancer and pharmaceutical properties of these natural compounds, indicating their potential as targeted cancer-killing agents, hops' chalcones have limited bioavailability due to their low solubility, which is an essential issue to explore their full potential as pharmaceutical drug candidates and may open the way for clinical trials [141]. For example, since the most consumed, orally ingested, prenylated chalcone, xanthohumol, is usually poorly absorbed and rapidly metabolized in inactive substances and excreted, thus limiting its bioavailability, clinical studies based on useful delivery forms for xanthohumol, such as micellar formulations of such hops/spent-hops' phytochemicals, have shown improved bioavailability and thus their pharmaceutical bio-functionality for xanthohumol [146].

Apart from the improved pharmacological efficacy of xanthohumol by such carriers, it has also been found that incorporation of bioactive hop compounds like xanthohumol in biomaterials composed of biopolymers, such as curdlan (linear 1,3-β-d-glucan) based hydrogel biomaterials, significantly enhanced the cosmeceutical bio-efficacy and biomedical potential of xanthohumol too, especially in the context of skin wound healing and regeneration [147]. It was also shown that the improved curdlan-based biomaterials with low concentrations of hop compounds (crude extract of xanthohumol) possess satisfactory hydrophilicity, wettability, porosity, and absorption capacities, while in vitro tests showed that these biomaterials were non-cytotoxic, did not inhibit the proliferation of skin fibroblasts, and had the ability to inhibit the production of pro-inflammatory interleukin-6 by human macrophages stimulated with lipopolysaccharide. Moreover, in vivo studies on the *Danio rerio* larvae model showed that these biomaterials were biocompatible and could promote the regeneration process after injury.

Overall, BSH could be converted into valuable ingredients with numerous applications in the food and beverages industry, pharmaceuticals, and cosmetics. For example, hop extracts have succesfully been used for treating acne, loose skin, stretch marks, and sagging, preventing skin aging (anti-inflammatory and antioxidant effects), whitening properties (intracellular tyrosinase and melanin inhibition and inhibition of melanogenesis and targeting melanin export and melanin degradation), as mouthrinse (containing 0.1% hops bract polyphenols), and as hair cosmetics, and deodorant effect and antimicrobial activities have also been reported [135]. Although there is limited scientific data related to the application of hop ingredients in skin products, the properties described for hop plant extracts or brewery by-products and also for their active compounds makes hops a promising ingredient for skincare cosmetics. Reusing brewery by-products instead of disposing of them aligns with challenging yet environmentally sustainable goals. Collaboration of scientists with breweries may efficiently yield sustainable results.

However, some studies suggest occupational dermatitis related to hop harvesting, and there are some questions about oral animal ingestion. This point must also be better explored before proposing any extract or component as a cosmetics ingredient. In this context, the extracts or isolated compounds must be in line with the Cosmetics Regulation related to the safety of cosmetics ingredients (EC 1223/2009) and also the Directive 2004/24/EC if the natural ingredients are used as herbal medicinal products. The regulations refer to the choice of the ingredients, manufacturing (according to Good Manufacturing Practices), and product commercialization, while they also ensure the safety of the product and compliance with the Cosmetics Regulation requirements by a specific person or company who places the cosmetic product on the market and is designated as responsible that the product ensures such requirements.

5. Conclusions

Beer, among other fermented drinks, has been consumed lavishly for centuries, and its by-products have traditionally been utilized, mainly as animal feed or as fertilizers. Recent studies have unveiled the anti-inflammatory health benefits of beer and its wastes. These products have shown antioxidant, anti-inflammatory, anti-thrombotic, cardio-protective, and neuroprotective properties. A wide range of bioactives have been identified in both beer and its by-products, including polyphenols, namely hop bitter acids, iso α-acids, prenyl flavonoids, and tyrosol, which have demonstrated antioxidant, neuroprotective, and cardio-protective properties. Notably, a substantial portion of the health benefits attributed to brewing products appears to be linked to the high concentration of xanthohumol, which has exhibited anti-inflammatory, anti-obesity, anti-proliferative, and neuroprotective effects. Additionally, beer and brewing by-products contain bio-functional polar lipids rich in UFA, which, even though they are present in minimal quantities in beer, they exhibit significant bioactivity, including anti-thrombotic and anti-platelet activating factor properties when studied *in vitro*. Among beer bioactive lipids, glycolipids, phosphatidylcholine, and phosphatidylethanolamines have shown notable effects.

The main future focus is on producing functional beverages, foods, nutraceuticals, and cosmetics that integrate the beneficial constituents of beer and its by-products. This strategy aims to utilize such products not only for promoting global health advantages, but also preventing inflammatory-linked diseases. Nevertheless, more *in vivo* testing for the biological efficacy and safety of novel products based on bioactive ingredients from beer and its by-products are needed, which, if combined with sensory evaluations for the consumers' perspectives on these novel products, they will provide a full evaluation of such novel products prior to their release in the market.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization, A.T.; writing—original draft preparation, A.T. and E.P.; writing—review and editing, all authors; visualization, A.T.; supervision, A.T.; project administration, A.T. All authors have read and agreed to the published version of the manuscript.

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