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Review Article

Bioactive phytochemicals in barley



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ABSTRACT

Epidemiological studies have consistently shown that regular consumption of whole grain barley reduces the risk of developing chronic diseases. The presence of barley fiber, especially β -glucan in whole grain barley, has been largely credited for these health benefits. However, it is now widely believed that the actions of the fiber component alone do not explain the observed health benefits associated with the consumption of whole grain barley. Whole grain barley also contains phytochemicals including phenolic acids, flavonoids, lignans, tocopherols, phytoosterols, and folate. These phytochemicals exhibit strong antioxidant, antiproliferative, and cholesterol lowering abilities, which are potentially useful in lowering the risk of certain diseases. Therefore, the high concentration of phytochemicals in barley may be largely responsible for its health benefits. This paper reviews available information regarding barley phytochemicals and their potential to combat common nutrition-related diseases including cancer, cardiovascular disease, diabetes, and obesity.

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1. Introduction

Barley is among the most ancient cereal crops grown in the world today. Archeological evidence suggests the existence of barley in Egypt along the River Nile around 17,000 years ago [1]. It is one of the top most cultivated crops globally (12% of total cereal cultivated), ranking fourth among cereal grains after wheat, rice, and maize [2]. Barley outperforms other cereals under various environmental stresses due to its winter-hardy, drought-resistant, and early maturing nature and is thus generally more economical to cultivate [3]. Approximately 65% of cultivated barley is used for animal feed, 33% for malting, whereas only 2% is used directly for human

consumption [4]. In 2014, over 48 million hectares of barley were cultivated globally, generating a harvest of 144 million metric tons, with the United States producing 3.8 million tons on 988,660 hectares of land during this period [5].

Epidemiological studies have associated the regular consumption of barley with its potential to reduce the risk of certain diseases, such as chronic heart disease [4,6,7], colonic cancer [8,9], high blood pressure [10], and gallstones [11,12]. Reports of barley's role in maintaining a healthy colon [13], inducing immunostimulation [14], and generally boosting the immune system [15], among others, have been established. These therapeutic potentials are attributed to the presence of the bioactive components of vitamins, minerals, fiber, and

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other phytochemicals. Interestingly, among the myriads of bioactive substances present in barley, fiber component, especially β -glucan fiber, is mainly credited for barley's health benefits [16–18].

Dietary fiber is a significant contributor to the health benefits of barley; however, sufficient evidence supports that phytochemicals also play important roles in preventing the development of chronic diseases [19]. Different classes of phytochemicals have been recognized, and their specific bioactivities have been reported. The major phytochemicals in barley that have shown health benefits include phenolic acids, flavonoids, lignans, vitamin E (tocols), sterols, and folates [20]. Phenolic compounds provide essential functions in reproduction and growth, act as defense mechanisms against pathogens, parasites, and predators, as well as contribute to the color of plants [21–23]. Sterols and tocols are mainly components of plant oils that provide benefits such as protection against toxins, neurological diseases like Alzheimer's disease, and diabetes [24,25]. Barley competes well with other major cereal grains, such as wheat, oat, rye, and rice in terms of content and diversity of phytochemicals. In addition, barley has some unique phytochemical properties, such as the presence of all eight tocol vitamers, which are usually not complete in some cereals [26–28].

Considering the high beneficial potential of phytochemicals on human health and the absence of a critical review regarding the subject in barley, we summarized the recent findings about the phytochemical components of barley and their ability to modulate parameters related to human health, analyzed the limitations and ideas of recent studies, and proposed directions for future research.

2. Phytochemicals in barley

Barley contains an assortment of phytochemicals (non-nutrient components) in varying concentrations usually determined by genotypic or environmental factors, or the interaction of both factors [20]. Phytochemicals in barley may exist in free, conjugated, or bound forms and are categorized into several major classes, including phenolic acids, flavonoids, lignans, tocols, phytosterols, and folates [29].

2.1. Phenolic acids

Phenolic acids (Figure 1), the dominant phenolic group of phytochemicals in barley are primarily located in the outer layers of the kernel [22]. They are subdivided into two groups: benzoic acid and cinnamic acid and their derivatives (Figure 1) [30–33]. Phenolic acids have been linked to chronic disease prevention partly due to the presence of unsaturated carboxylic group [34]. The abundant content of phenolic acids in barley, especially in the hulled variety, indicates that it may also serve as an excellent dietary source of natural antioxidants with antiradical and antiproliferative potentials [30,35].

In barley, phenolic acids are found at highest concentrations in the bound form, followed by conjugated and free forms, respectively [31]. The free forms are often located in the outer part of the pericarp, whereas the bound forms are

esterified to cell wall constituents, such as lignin, cellulose, arabinoxylans, polysaccharides, and hemicelluloses [36]. Free phenolic acids are usually a small portion of the total phenolic acid concentration. The phenolic acid concentration in barley approximately ranges between 4.6 $\mu\text{g/g}$ and 23 $\mu\text{g/g}$ for the free form, between 86 $\mu\text{g/g}$ and 198 $\mu\text{g/g}$ for the conjugated form, and between 133 $\mu\text{g/g}$ and 523 $\mu\text{g/g}$ for the bound form, whereas the total phenolic acid concentration ranges between 604 $\mu\text{g/g}$ and 1346 $\mu\text{g/g}$ [32,37]. The free forms of the major phenolic acids in barley are ferulic acid (FA; 27% of dry matter), vanillic acid (28%), syringic acid (17%), and *p*-coumaric acid (22%) [38].

FA is the most abundant and the main low molecular weight phenolic acid in barley [39]. It accounts for approximately 68% of total phenolic acids in barley, and its concentration in barley grains ranges between 149 $\mu\text{g/g}$ and 413 $\mu\text{g/g}$ [40]. Andersson et al [39] reported that the total concentration of FA in barley is about 270 $\mu\text{g/g}$ of dry matter, whereas the average total concentrations of free, conjugated, and bound FA for different varieties of barley were approximately 2.7 $\mu\text{g/g}$, 33.21 $\mu\text{g/g}$, and 235 $\mu\text{g/g}$, respectively [39]. The major dehydromers of FA in barley are the (Z)- β -[4-[(E)-2-carboxyvinyl]-2-methoxyphenoxy]-4-hydroxy-3-methoxycinnamic acid (8-O-4'-DiFA), (E,E)-4,4'-dihydroxy-5,5'-dimethoxy-3'-bicycinnamic acid (5,5'-DiFA) trans-5-[(E)-2-carboxyvinyl]-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxylic acid (8,5'-DiFA benzofuran form), and (E,E)-4,4-dihydroxy-3,5'-dimethoxy- β ,3'-bicycinnamic acid (8,5'-DiFA open form) (Figure 1). Among barleys FA dehydromers identified [41], 8-O-4'-DiFA (73–118 $\mu\text{g/g}$ dry weight) was the major dehydromer, followed by 5,5'-DiFA (26–47 $\mu\text{g/g}$), 8,5'-DiFA benzofuran form (22–45 $\mu\text{g/g}$), and 8,5'-DiFA open form (10–23 $\mu\text{g/g}$) [41]. *p*-Coumaric acid is the second most abundant phenolic acid in barley ranging from 15 $\mu\text{g/g}$ to 374 $\mu\text{g/g}$ [32]. The concentrations of different forms of individual phenolic acids in barley expressed based on dry weight are presented in Table 1.

2.2. Flavonoids

Flavonoids (Figure 2) are phytochemical compounds with a $\text{C}_6\text{-C}_3\text{-C}_6$ skeleton (2 aromatic rings joined by a 3-carbon link). They are also believed to be UV-B absorbing compounds [42], which provide protection against UV radiation in response to “excess light” stress [43,44]. Clinical studies indicate that flavonoids may be the bioactive substances present in cereal grains responsible for the moderation of many diseases including cancer and coronary heart diseases [36,45].

Flavanols, anthocyanins, and proanthocyanidins (polymers of flavonoids) are the major types of flavonoids found in barley grains. Flavanols and anthocyanins are located in the pericarp of barley grains where they exist mostly as glycoside derivatives, including cyanidin-3-glucoside, penidin-3-glucoside, and delphinidin-3-glucoside [37,46]. Generally, the content of flavonoids in barley grains are proportional to the degree of color depth, and blue and purple barley grains have been discovered to possess the most flavonoid content among barley varieties [47].

Kim et al [48] studied the flavonoid content of 127 lines of hulled and unhulled colored barley wherein the total

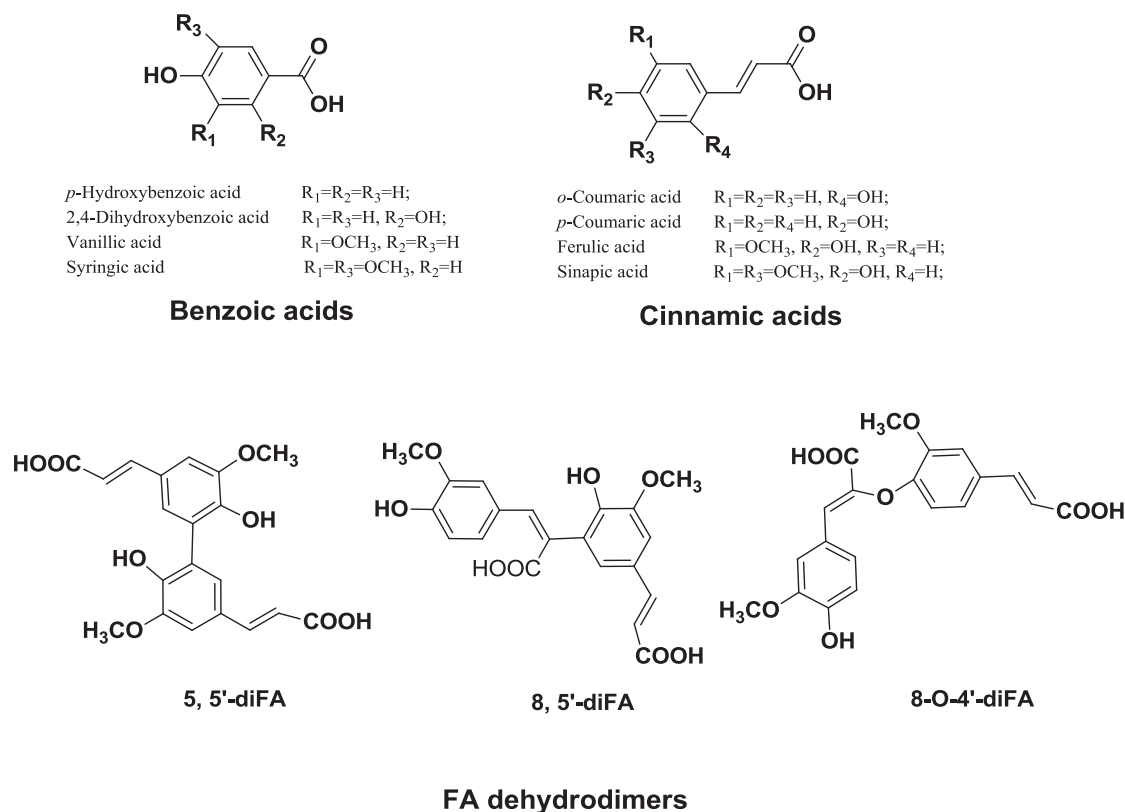


Figure 1 – Structures of major phenolic acids in barley. FA = ferulic acid.

Table 1 – Content and composition of total, free, conjugated, and bound phenolic acids in barley.

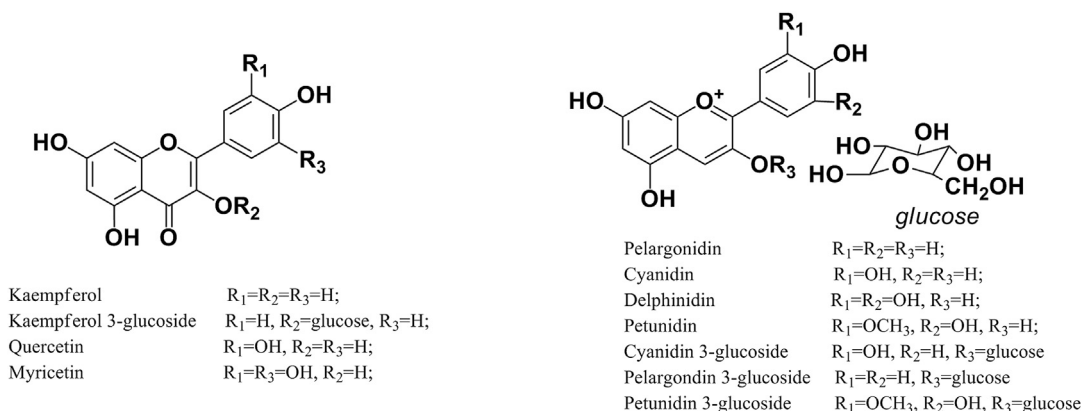
Phenolic acids	Free form (μg/g)	Conjugated form (μg/g)	Bound form (μg/g)
<i>p</i> -Hydrobenzoic acid	n.d.	5.8–26.7	0.5–5.4
Vanillic acid	1.45–4.71	8.9–30.2	0.5–7.5
Syringic acid	0.45–3.74	2.2–10.0	0.0–3.0
2,4-Dihydroxybenzoic acid	0.04–2.62	6.8–61.8	11.1–74.4
Sinapic acid	n.d.	12.4–24.4	8.9–17.8
Ferulic acid	1.32–5.87	21.7–42.5	104.3–365.4
<i>p</i> -Coumaric acid	0.57–7.01	1.7–13.1	2.7–109.7
<i>o</i> -Coumaric acid	0.27–1.31	1.2–3.2	2.7–4.7

Note. From “Phytochemical and dietary fiber components in barley varieties in the HEALTHGRAIN diversity screen,” by Andersson et al, *J Agric Food Chem*, 56, p. 9767–76. Copyright 2016, American Chemical Society. Adapted with permission.
 n.d. = not determined.

flavonoid content was found to range between 62.0 and 300.8 μg/g. Goupy et al [49] affirmed that monomeric, dimeric, and trimeric flavanol accounts for 58–68% of the total phenolic content of barley and that trimeric flavanols are the most abundant flavanols in barley. The proanthocyanidin content in barley studied by Kim et al [48] varied between

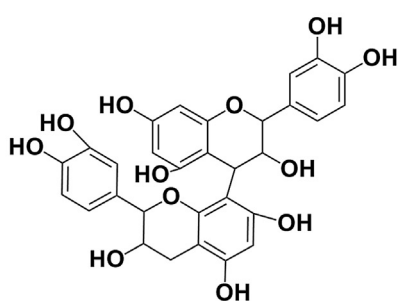
15.8 μg/g and 131.8 μg/g. The proanthocyanidin content of the unhulled barley group (75.9 μg/g) was higher than that of the hulled group (56.29 μg/g), whereas the proanthocyanidin content of the blue and purple group (83.0 μg/g) was significantly higher than that of the black group (55.3 μg/g). In a related study, Dvorakova et al [50] examined the proanthocyanidin content of 10 barley varieties (8 malt and 2 hullless barley varieties). From that study, the major proanthocyanidins reported included two proanthocyanidin dimers (prodelphinidin B3 and procyanidin B3) and four proanthocyanidin trimers (procyanidin C2, prodelphinidin C2, and 2 other prodelphinidin isomers). Prodelphinidin B3 (90–197 μg/g) accounted for majority of proanthocyanidin present in barley, whereas procyanidin C2 (5–19 μg/g) was reported to be present only in minor quantities [50].

Anthocyanins are water-soluble vacuolar pigments and the most studied flavonoids in barley. They are mainly present in the pericarp or the aleurone layers of barley grain causing purple or blue hues of kernel color. Anthocyanins in barley include cyanidin, cyanidin 3-glucoside, delphinidin, pelargonidin, pelargonidin glycosides, and petunidin 3-glucoside [46,51]. The most common anthocyanin in purple barley is cyanidin 3-glucoside (214.8 μg/g), followed by peonidin 3-glucoside and pelargonidin 3-glucoside. These three anthocyanins account for 50–70% of total anthocyanins reported in barley. Delphinidin 3-glucoside is usually the most abundant anthocyanin in blue (167.6 μg/g) and black (36.0 μg/g) barley varieties. In general, purple and blue barley (320.5 μg/g)

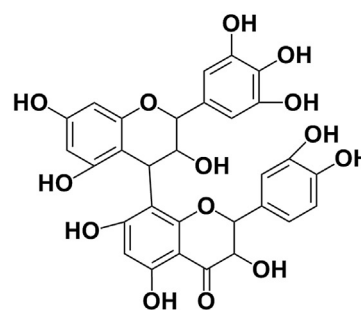


Flavonols

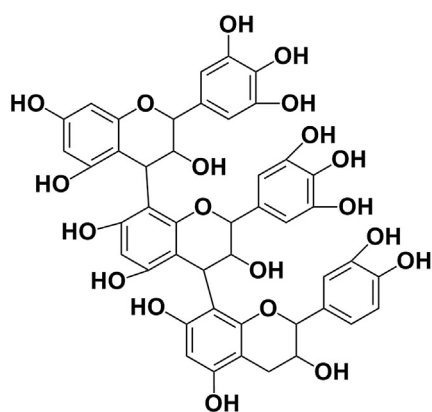
Anthocyanidins/Anthocyanins



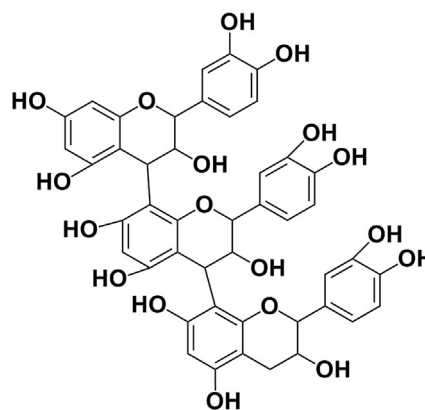
Procyanidin B3



Prodelfphinidin B3



Prodelfphinidin C2



Procyanidin C2

Proanthocyanidins

Figure 2 – Structures of major flavonoids in barley.

contain higher average concentrations of anthocyanins than black barley (49.0 $\mu\text{g/g}$) [52,53]. Jende-Strid [54] reported that delphinidin and cyaniding were present in yellow, blue, and black barley varieties, whereas pelargonidin was present in purple barley.

Yang et al [55] analyzed the profiles of common flavonoids in unhulled purple barley, normal barley, and hulled purple barley. The bran-rich fraction of barley grain contained the most flavonoid content, whereas the hull fraction did not contain any significant flavonoid content. The total average

content of flavonoids in hulled purple barley (124.8 $\mu\text{g/g}$) was significantly higher than that in unhulled purple barley (69.40 $\mu\text{g/g}$) and normal barley (48.50 $\mu\text{g/g}$). Total concentrations of catechin in the three types of barley studied varied from 0 $\mu\text{g/g}$ to 21.85 $\mu\text{g/g}$. The total average catechin content in whole grain normal barley was significantly higher than that in hulled purple barley and unhulled purple barley. Whole grain myricetin content in hulled purple barley was significantly higher than that in unhulled purple barley and normal barley. The total average content of quercetin in hulled purple barley (60.98 $\mu\text{g/g}$) was significantly higher than that in the unhulled purple barley (24.35 $\mu\text{g/g}$) and normal barley (0.00 $\mu\text{g/g}$). The total average kaempferol content in unhulled purple barley (36.00 $\mu\text{g/g}$) was considerably higher than that in hulled purple barley (32.56 $\mu\text{g/g}$) and normal barley (26.65 $\mu\text{g/g}$).

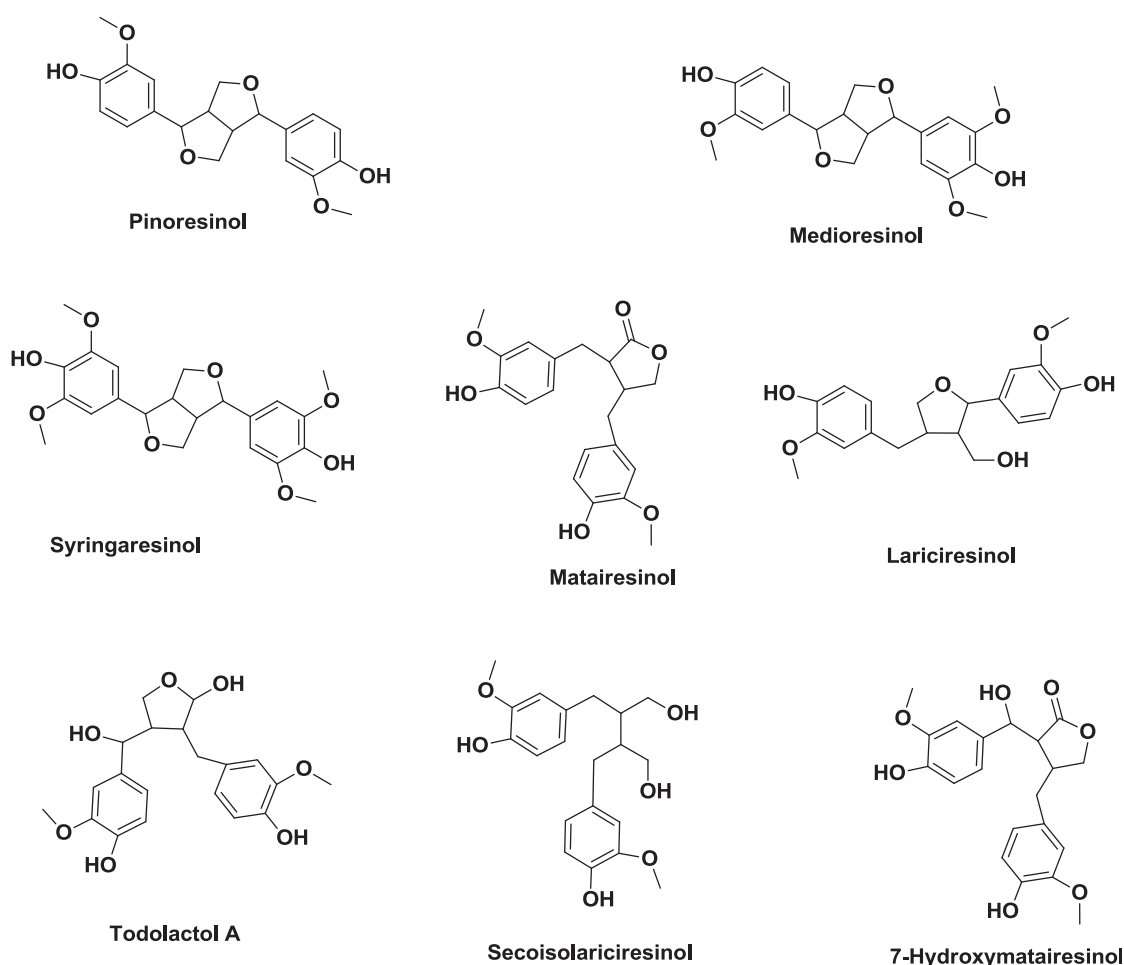
2.3. Lignans

Lignans (Figure 3) are natural polyphenols widely distributed in the plant kingdom as natural defense substances. They are bioactive as phytoestrogens because of their structural and functional similarity to 17 β -estradiol. Lignans have been

suggested to induce a wide range of biological effects, such as antioxidant, antitumor, antiviral, antibacterial, insecticidal, fungistatic, estrogenic, and antiestrogenic activities, and protect against coronary heart disease [56–58]. There is little information in the literature about lignans in barley. Smeds et al [59] studied the content of lignans in barley, which was reported to include pinoresinol (71 $\mu\text{g}/100\text{g}$), medioresinol (22 $\mu\text{g}/100\text{g}$), syringaresinol (140 $\mu\text{g}/100\text{g}$), lariciresinol (133 $\mu\text{g}/100\text{g}$), cyclolariciresinol (28 $\mu\text{g}/100\text{g}$), secoisolariciresinol (42 $\mu\text{g}/100\text{g}$), secoisolariciresinol-sesquillignan (24 $\mu\text{g}/100\text{g}$), matairesinol (42 $\mu\text{g}/100\text{g}$), oxomatairesinol (28 $\mu\text{g}/100\text{g}$), and 7-hydroxymatairesinol (541 $\mu\text{g}/100\text{g}$) as major lignans and todolactol (127 $\mu\text{g}/100\text{g}$), α -conidengrin acid (33 $\mu\text{g}/100\text{g}$), nor-trachelogenin (15 $\mu\text{g}/100\text{g}$), and lariciresinol-sesquillignan (6.6 $\mu\text{g}/100\text{g}$) as minor lignans.

2.4. Tocols

Tocopherols and tocotrienols (collectively known as tocols; Figure 4) are a class of lipid-soluble phytochemicals found in barley. Tocols are recognized for their antioxidant properties, especially their ability to inhibit lipid peroxidation in



Lignans

Figure 3 – Structures of major lignans in barley.

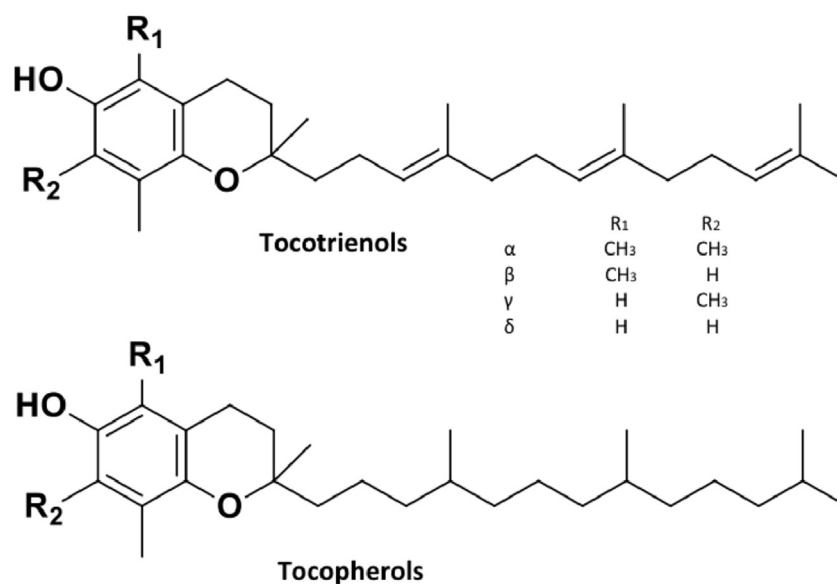


Figure 4 – Structures of major tocols in barley.

biological membranes [60–63]. In addition to their antioxidant properties, tocols found in cereals proffer anticancer and cancer suppression effects [64,65], induce the immune system [66], moderate the risk factors of cardiovascular diseases (CVD) [67,68], and promote apoptosis induction [69]. One of the most striking discoveries about tocols is their ability to clear atherosclerotic blockages (stenosis) in the carotid artery, potentially reducing the risk of stroke [70].

Barley is one of the best sources of tocols among cereals due to a high concentration and favorable distribution of all eight biologically active vitamers [71]. Moreau et al [71] reported that levels of total phytosterols and total tocotrienols in the oils prepared from both whole kernels and scarified fines of barley ranged between 2911 $\mu\text{g/g}$ and 6126 $\mu\text{g/g}$. This value is several-folds higher than that in palm oil (530 $\mu\text{g/g}$) and rice bran oil (770 $\mu\text{g/g}$), promoted as “high in tocotrienols”. Temelli et al [72] studied the total tocol content of whole grain barley varieties, which ranged between 40 $\mu\text{g/g}$ and 151.1 $\mu\text{g/g}$. In whole grain barley, α -tocotrienol is the most individual tocol isomer, contributing about 47.7% of the total tocol content [39], followed by α -tocopherol (17.7–33.9%), γ -tocotrienol (10.4–20.2%), γ -tocopherol (1.9–9.2%), β -tocotrienol (2.9–7.8%), and δ -tocotrienol (2.7–6.7%) [72]. The average content of tocotrienol in barley is about 70.6–76.8% [40,71]. This signifies that barley could be one of the richest sources of tocotrienol among cereal grains.

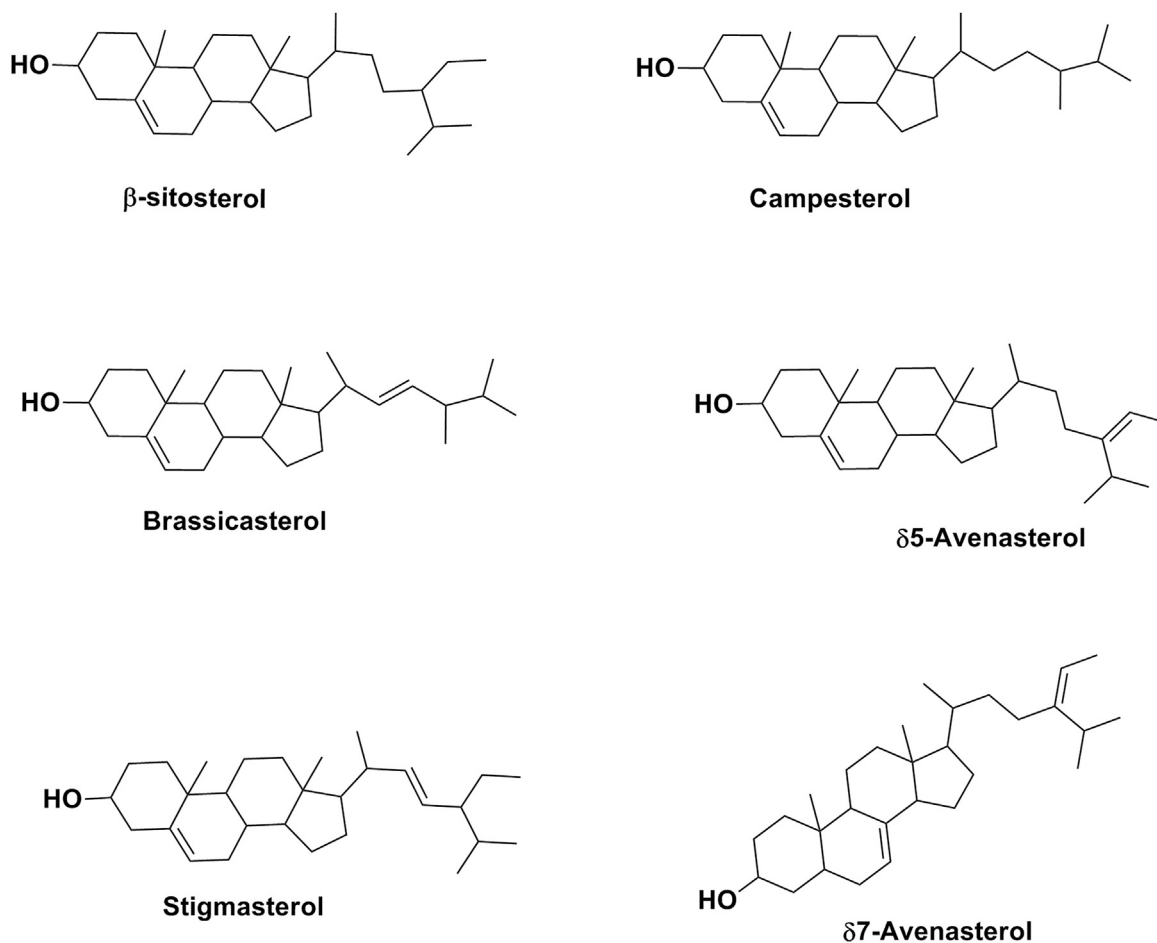
The majority of barley's tocopherols are located in its germ fraction, whereas the tocotrienols are mostly present in the endosperm and pericarp fraction of barley grains. Zielinski [28] reported that 95% of tocols occur in the endosperm, whereas 63% and 10% of tocols occur in the hull and germ components of barley, respectively. Hulled barley has been reported to possess more tocol content than hullless barley. Cavallero et al [73] reported higher tocol and α -tocotrienol contents in hulled barley (53–61 $\mu\text{g/g}$) than those in hullless barley (50.9–53.1 $\mu\text{g/g}$). This is attributed to the presence of tocols in the hull of barley. However, a study by

Ehrenbergerova et al [74], showed that the hullless waxy variety, Washonubet, had a statistically higher total content of tocols (67.6 $\mu\text{g/g}$) and α -tocotrienol isomer (42.1 $\mu\text{g/g}$) than all other barley varieties studied, including hulled varieties. This gives credence to the variation between genotypes and the effect of growing location on tocol content.

2.5. Phytosterols

Phytosterols (Figure 5) or plant sterol is an important structural component of plant membrane similar in structure to cholesterol, but different in configuration. Recent studies have shown that natural intake of dietary plant sterols can have a positive effect in decreasing serum cholesterol levels, protect against CVD, and prevent colon cancer [75–80]. Cereals are the main source of plant sterols, together with vegetable oils, contributing up to 40% of daily intake of plant sterols [81].

Barley is considered a good source of phytosterol although barley's phytosterol level is moderate compared with other major grains [82]. Barley grains generally contain phytosterols in both free and bound forms, esterified to fatty acids, phenolic acids, steryl glucosides, or acylated steryl glycosides. The level of esterification varies among varieties and around different parts of barley grain [83]. Higher levels of phytosterols have been identified in the outer layers of the kernel. The content of sterols in 10 barley varieties studied by Andersson et al [39] ranged between 820 $\mu\text{g/g}$ and 1153 $\mu\text{g/g}$. Piironen et al [84] analyzed and compared the phytosterol content of major cereal grains with the highest plant sterol content (mean, 955 $\mu\text{g/g}$) determined in rye, followed by barley (761 $\mu\text{g/g}$), wheat (690 $\mu\text{g/g}$), and oat (447 $\mu\text{g/g}$). As in most cereals, sitosterol is the most abundant sterol form in barley, contributing about 53–61% of total sterols, followed by campesterol (14–20%). Other reported forms of sterol in barley include brassicasterol, stigmasterol, δ 5-avenasterol, stigmastenol, stigmastadienol, and δ 7-avenasterol [85]. Lampi et al



Phytosterols

Figure 5 – Structures of major phytosterols in barley.

[85] studied the concentration of individual sterols in barley whole grain; β -sitosterol ($476 \pm 1 \mu\text{g/g}$) was the most abundant, followed by campesterol ($181 \pm 2 \mu\text{g/g}$), stigmasterol ($39 \mu\text{g/g}$), and other minor sterols (δ 5- and δ 7-avenasterols, δ 7-stigmasterol, and stigmastadienol; $86 \pm 1 \mu\text{g/g}$).

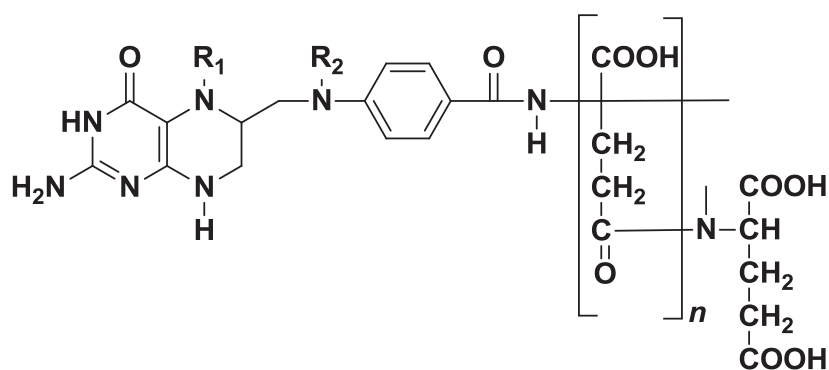
The fully saturated subgroup form of phytosterol (phytostanols) has also been reported in barley; however, its concentration is generally lower than that of unsaturated sterols. The major phytostanols in barley are sistostanol and campestanol. According to Andersson et al [39], phytostanol makes up only about 1–3% of total phytosterol in barley. From that study, the concentration of phytostanol in 10 varieties of barley varied between 10–30 $\mu\text{g/g}$. Lampi et al [85] recorded the stanol concentrations of campestanol (11 $\mu\text{g/g}$) and sitostanol (5 $\mu\text{g/g}$) for the variety of barley studied.

2.6. Folates

Folate (Figure 6) is a group of phytochemicals that represents an essential nutrition component (vitamin B). Folate is capable of performing the same biological activity as folic acid and is

involved in many metabolic pathways [86]. Cereals are considered an important source of folate, though little is known about folate in barley. Folate is thought to be unevenly distributed in barley grain with more concentration around the outer layers than around the endosperm [87]. Edelman et al [88] studied the distribution of folates in barley grain, which was found to accumulate in the bran and germ tissues of the grain. Andersson et al [39] studied the total folate content of 10 barley genotypes (518–789 ng/g of dry mass), which was found to be higher than that of wheat (323–774 ng/g, $n = 130$) [89], oat (495–604 ng/g, $n = 5$) [90], and close to that of rye (574–775 ng/g, $n = 10$). Edelman et al [88] also reported a similar folate content of 598–664 ng/g for five hulled Finnish barley cultivars studied.

The comparison between the occurrence and proportions of folate vitamers is difficult among cereal grain samples because of differences in the analytical methods and number of examined vitamers. Moreover, the harvesting time, growing conditions, and storage time may have an effect on the vamer pattern. However, folate vitamers reported in barley include 5-methyltetrahydrofolate (5-HCO-H₄folate), 5,



H ₄ folate	R ₁ =R ₂ =H;
5-HCO-H ₄ folate	R ₁ =CHO, R ₂ =H;
10-HCO-H ₄ folate	R ₁ =H, R ₂ =CHO;
5-CH ₃ -H ₄ folate	R ₁ =CH ₃ , R ₂ =O;
5,10-CH ₂ -H ₄ folate	R ₁ --R ₂ --CH ₂ -;
5,10-CH ⁺ -H ₄ folate	R ₁ --R ₂ = ⁺ CH-;
<i>n</i> ranged from 1 to 8;	
– refers to connection between R ₁ and R ₂	

Folates

Figure 6 – Structures of major folates in barley.

10-methylenetetrahydrofolate (5-CH₃-H₄folate), 5, 10-methenyl- tetrahydrofolate (5, 10-CH⁺-H₄folate) and 10-formylfolic acid (10-HCO-PGA). Edelman et al [88] found the major folate vitamer in barley to be 5-HCO-H₄folate, which contributed an average of 27–42% of total folate content, followed by 5-CH₃-H₄folate and 10-CH⁺-H₄folate. The proportion of 10-HCO-PGA was remarkable in the industrial milling fractions studied, with contributions of an average of 9–22% of total folate content.

3. Barley phytochemicals and human health

3.1. Cardiovascular disease (CVD)

CVD is a leading cause of death in the United States [91]. In 2011, the overall death rate attributed to CVD was 229.6 per 100,000 Americans, and in 2013, coronary heart disease alone caused approximately one of every seven deaths in the United States [92]. It is generally recognized that high blood cholesterol level is a significant risk factor in the occurrence of CVDs. In addition, there is evidence indicating that free radicals and other oxidants largely cause most neurodegenerative diseases linked with CVDs, such as Alzheimer's disease and stroke [93–96]. Consumption of natural antioxidants, such as polyphenols, in daily diets can produce an effective protective action against oxidative processes generated by these compounds, thereby improving cardiovascular health [97–100].

Recent strategies for reducing the risk of CVDs utilize dietary restrictions to limit cholesterol intake and/or the use of a class of medication, statin, to lower serum cholesterol. Barley

kernels are rich in phytosterols and are important for cardiovascular health. Consumption of barley grains rich in phytonutrients may help reduce the dependence on drug use or dietary restrictions for the moderation of CVD. Barley phytosterols can compete with cholesterol for micelle formation in the lumen of the intestine, thus inhibiting cholesterol absorption and increasing secretion and regulation of cholesterol levels. Studies show that the levels of total phytosterols in barley oils are sufficient (0.18–1.44 g/15 g oil) to significantly lower low-density lipoprotein (LDL) cholesterol at reasonable dosages of 15 mL/d (1 tablespoon/d) [71].

Polyphenols also play a major role in moderating CVDs due to their antiradical scavenging potential. Polyphenols extracted from black highland barley were found to have strong superoxide radical, hydroxyl radical, 2,2-diphenyl-1-picrylhydrazyl radical-scavenging activity, and antioxidant ability. Mice that were administered 600 μg black highland polyphenol extract per gram body weight showed significant reduction in total cholesterol (23.33%), LDL cholesterol (26.29%), and atherosclerosis index (38.70%), in addition to increasing high density lipoprotein cholesterol (HDL, 17.80%) [101]. Lee et al [102] also reported that barley sprout extract containing polyphenols regulated AMP-activated protein kinase, a cellular sensor of energy metabolism and a regulator for cholesterol metabolism. The barley sprout extract containing 19.65 mg/g of total polyphenol concentration reduced the intracellular total and free cholesterol concentrations in mice by 24% and 18%, respectively. Lignans, also present in barley, have been found to act as strong antioxidants comparable to FA and better than vitamin E [103]. They have also been reported to lower the risk of CVD [104].

Tocotrienols and tocopherols in barley are strong antioxidants and thought to be important for cardiovascular health. Among the most economically important cereals (wheat, barley, rice, rye, and oat), barley has been reported to have the highest amounts of tocopherols and phytosterols [39,87,105]. Tocopherols have been reported to lower serum cholesterol in humans and chicks [106]. Qureshi et al [107] identified α -tocotrienol as an inhibitor of cholesterol biosynthesis in the livers of experimental animals. The mechanism for this effect was α -tocotrienol's ability to suppress 3-hydroxy-3-methyl-glutaryl-coenzyme reductase, a rate-limiting enzyme involved in cholesterol biosynthesis. Burger et al [108] reported that the administration of 0–20 ppm α -tocotrienol from barley for a 3-week period controlled the biosynthesis of cholesterol concentrations and reduced cholesterol levels by approximately 60%. Nonetheless, there have been conflicting reports on the ability of barley tocopherols to moderate cholesterol levels. Earlier data presented by Jadhav et al [109] showed no effect of barley oil on total serum cholesterol in rats fed a diet based on potato starch. Wang et al [106] also found no evidence in support of the cholesterol-lowering effect of barley oil and its nonsaponifiable constituents with the hamster model.

Folate has been associated with cardiovascular health. It is currently one of the most studied vitamins due to its essential role in amino acid metabolism and DNA methylation. It functions as a coenzyme, providing a carbon unit of nucleotide biosynthesis in humans. Its suboptimal presence in humans has been associated with the increased risk of cardiovascular ailment [110,111]. Barley grains enriched with folate are, therefore, a good and natural means of obtaining folate from diets and in turn preventing and reducing the risk of cardiovascular ailments.

3.2. Diabetes and obesity

Diabetes and obesity are public health problems with health and economic consequences that have raised global concern. Cost-effective mitigation strategies rather than containment are, therefore, of paramount importance for the prevention and treatment of these diseases. As a result, a plethora of lifestyle modification, diets, pills, and weight loss regimens have been recommended. Several epidemiological studies have linked the consumption of barley with the reduction of diabetes and obesity [112,113]. Nonetheless, the components of barley responsible for these benefits have not been clearly identified, but fiber and high nutrient components are considered leading contenders.

Notwithstanding scarce *in vivo* studies on effects of barley phytochemicals on diabetes and obesity, it is well known that one of the primary pathogenic factors leading to insulin resistance, β -cell dysfunction, impaired glucose tolerance, and ultimately diabetes occurrence is oxidative stress. Oxidative stress, which plays an important role in the pathology of diabetes and obesity, can be moderated by phytochemicals present in barley. An increase in the formation of reactive oxygen species and a decrease in antioxidant defense efficiency are characteristics of both diseases [114–116]. Therefore, phytochemicals may prevent the development and progression of obesity and diabetes by reducing oxidative stress [117]. Barley phytochemicals that may have a role in

protecting against diabetes and obesity include various phenolic acids, flavonoids, phytosterols, and tocopherols. These compounds function as strong antioxidants. However, total phenolic acids are considered as the major components responsible for the antioxidative benefits of cereals including barley [38,118]. Phenolic acids in cereals have demonstrated similar or higher antioxidative activities than catechins and have been linked to prevention of chronic disease due to the presence of unsaturated carboxylic group [119]. Zielinski and Kozłowska [120] reported a positive correlation coefficient value of 0.96 between total phenolic compounds and total antioxidative activity of 80% methanolic extracts of barley whole grains. Goupy et al [49] studied the antioxidative properties of barley phytochemicals. The antioxidative properties of barley flavonoids, phenolic acids (especially FA), and tocopherols (α , β , γ) determined by their capacity to react with 2,2-diphenyl-1-picrylhydrazyl (DPPH) were approximately 4.76, 0.34, and 0.89 antiradical power, respectively. In addition, the antioxidative activity determined by the inhibition of cooxidation of β -carotene in linoleate model system for different barley flavonoids studied ranged from 16.4% to 65.5%, whereas those for phenolic acids ranged from 12% to 31.2% and those of tocopherol ranged from 49.1 to 55.2%. Antioxidative activities of barley were also studied by their ability to inhibit lipoxygenase. The antioxidative activities recorded were 24.8–65.4% for flavonoids, 2.9–10.8% for phenolic acids, and 49.1–63.9% for tocopherols. Carotenoids in barley didn't show as high antioxidant activities as other phytochemicals such as flavonoids and phenolic acids.

The antioxidative activity investigated for 80% methanolic extracts originating from different whole grains were in the hierarchy: barley > oat > wheat > rye [120]. This high antioxidative activity of phytochemicals present in barley makes it a useful natural means for the prevention of diabetes and obesity development and progression. Furthermore, systemic, low-grade inflammation, especially in adipose tissue, is a trademark of obesity and diabetes. In addition to barley phytochemicals' antioxidant properties, barley phytochemical compounds have potent anti-inflammatory actions and could thereby moderate diabetes and obesity risk by this mechanism [121–123].

3.3. Cancer

Epidemiological data indicate that diet/lifestyle is responsible for approximately 20–80% human cancer mortality [124]. Dietary factors, especially those that reduce the impact of reactive oxygen species, can protect against DNA damage and stimulate the immune system, thus lowering cancer risks [125]. Barley and its products have bioactive compounds with antioxidative and immunomodulatory activities that are associated with cancer moderation. Most studies regarding the chemoprevention of carcinogenesis by barley have been *in vitro* and have mainly involved the effect of barley fiber, especially β -glucan, and the moderation of this disease. Kanauchi et al [126] investigated anti-carcinogenic benefits of germinated barley foodstuff (GBF), a prebiotic heterogeneous mixture of approximately 80% hemicellulose and insoluble glutamine-rich protein fiber. GBF also contains phytochemicals, especially phenolic acids, present in free or bound forms

which contribute to its health benefits [127]. Kanauchi et al [126] reported that GBF affects the early stages of the pathogenesis of colon cancer and helps impede transforming hyperproliferative epithelia. GBF's administration when compared with the control diet, induced the production of acetate ($p < 0.05$) and increased the luminal short chain fatty acid concentration, especially butyrate ($p < 0.05$), which is produced in the colon. The colonic mucosa of F344 rats in the GBF group showed a decrease in the production of succinate ($p < 0.05$) and a reduction in the expression of β -catenin ($p < 0.05$), aberrant crypt foci ($p < 0.05$), and β -catechin formations ($p < 0.05$). The activities of slc5a8, a tumor suppressor gene and a solute carrier, cecal B-glycosidase, and heat shock protein 25 (HSP25) positive cells content also increased in the GBF group compared with those in the control group ($p < 0.05$). Studies regarding the moderation of colonic carcinogenesis have shown similar changes in the contents and activities of acetate, butyrate, succinate, HSP25 positive cells, β -catenin, aberrant crypt foci, and other related biomarkers [128–133]. In another report by McIntosh et al [134] on the influence of different fiber-rich sources from wheat and barley in diets on tumor incidence, tumor burden, tumor mass index, and dimethyl induced tumor, these were reported to be more effectively prevented by dietary insoluble fiber from barley than from other soluble fiber-rich commercial bran from barley and oat [134]. Spent barley grain, a by-product of the brewing industry, produced the lowest tumor incidence (70%), tumor mass index (1.20), and the tumor burden per 10 rats (13).

Emerging research also suggests that polyphenols may offer more health benefits, such as enhancement of endothelial function, improvement of cellular signaling, and crucial intestinal protection from undigested polyphenols associated with fiber, than previously thought [135]. The abundant content of phenolic compounds in barley suggests that it may also serve as an excellent dietary source of natural antioxidants with antiradical and antiproliferative potentials [35]. Several studies have shown that FA has tumor inhibition properties [136,137]. There have also been reports of its ability to inhibit large bowel carcinogenesis [138].

Although a positive relationship exists between the intake of phenolic compounds and the reduced risk of certain chronic diseases, it remains unclear whether the protective effect of phenolic compounds arises from antioxidant activity or other mechanism.

High antioxidant activity due to the presence of phenolic acids in barley were reported by Madhujith and Shahidi [139] and Bellido and Beta [52]. Barley extracts with high phenolic acid content and corresponding high antioxidative activity led to the inhibition of cell proliferation of Caco-2 colon cancer by 29.3–51.2% after the administration of 0.5 mg/mL and 0.05 mg/mL of phenolic extracts from barley. Fermentation of barley (lactic acid) was also reported to produce a novel purple pigment called hordeumin, a type of anthocyanidin–tannin pigment whose scavenging activity increases with the length of fermentation. Deguchi et al [140] suggested that the free radical activity of hordeumin results from barley bran polyphenols. Phytochemicals present in barley may be beneficial in moderating the risk factors associated with cancer and therefore should be a subject of further studies.

4. Conclusion

Barley has an assortment of phytochemicals with the potential to impact human health. These benefits are due to inherent properties present in phytochemicals, such as high antioxidative activity against different free radicals, anti-inflammatory, and immunostimulation potentials, or the ability to inhibit LDL cholesterol, while increasing HDL cholesterol levels. However, there is a need for more systemic and detailed study on barley phytochemicals, thus establishing a chemical profile for phytochemicals in barley and possibly identifying unique compounds as have been done with avenanthramides in oat and alkylresorcinols in rye and wheat. In addition, since specific studies on health effects of phytochemicals in barley are limited, it is worthwhile to further study the efficacy and the underlying molecular mechanisms of barley phytochemicals, thereby promoting the use of barley as a functional food.

Conflict of interest

The authors have no conflict of interest to declare.

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