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A comprehensive review of wheat phytochemicals: From farm to fork and beyond

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Abstract

The health benefits of whole wheat consumption can be partially attributed to wheat's phytochemicals, including phenolic acids, flavonoids, alkylresorcinols, carotenoids, phytosterols, tocopherols, and tocotrienols. It is of increasing interest to produce whole wheat products that are rich in bioactive phytochemicals. This review provides the fundamentals of the chemistry, extraction, and occurrence of wheat phytochemicals and includes critical discussion of several long-lasting issues: (1) the commonly used nomenclature on distribution of wheat phenolic acids, namely, soluble-free, soluble-conjugated, and insoluble-bound phenolic acids; (2) different extraction protocols for wheat phytochemicals; and (3) the chemistry and application of in vitro antioxidant assays. This review further discusses recent advances on the effects of genotypes, environments, field management, and processing techniques including ultrafine grinding, germination, fermentation, enzymatic treatments, thermal treatments, and food processing. These results need to be interpreted with care due to varied sample preparation protocols and limitations of in vitro assays. The bioaccessibility, bioavailability, metabolism, and potential health benefits of wheat phytochemicals are also reviewed. This comprehensive and critical review will benefit scientific researchers in the field of bioactive compounds of cereal grains and also those in the cereal food industry to produce high-quality functional foods.

KEYWORDS
alkylresorcinols, antioxidants, cereal nutrients, health benefits, phenolic acids, wheat phytochemicals

1 | INTRODUCTION

Whole grains were defined by the American Association of Cereal Chemists (AACC) International in 1999 and adopted by the U.S. Food and Drug Administration (FDA) in 2006 as consisting of the "intact, ground, cracked or flaked fruit of the grain whose principal components, the starchy endosperm, germ and bran, are present in the same relative proportions as they exist in the intact grain" (FDA, 2006). Epidemiological studies have found that consumption of whole grain products may reduce the risk of chronic diseases such as obesity, type 2 diabetes, cardiovascular diseases (CVDs), and cancer (Benisi-Kohansal et al., 2016). The health-promoting effects of whole grain products, such as whole wheat products, can be attributed to their dietary fiber (DF) and phytochemical constituents (Okarter & Liu, 2010). Driven by consumer demand for healthy food ingredients and products, wheat breeders and producers are becoming interested in phytochemicals as another quality parameter for wheat evaluation in addition to conventional end-use properties (Shewry et al., 2012).

The past two decades have witnessed significant progress in research on wheat phytochemicals in the following aspects: (1) chemistry and distribution; (2) effect of genotypes, environments, and management; (3) effect of grain and food processing; (4) bioavailability; and (5) health benefits (Figure 1). For example, phenolic acids, flavonoids, alkylresorcinols, carotenoids, tocopherols and tocotrienols, phytosterols, benzoxazinoids (BXs), and other bioactive compounds in whole grains have been isolated and characterized (Figures 2–4; Tables 1 and 2). Wheat phytochemicals' relationship with genetic variations, environment, and field management has been extensively described. Changes in wheat phytochemicals during grain treatment and food processing have been investigated. Various processing technologies have been developed to increase the nutraceutical value of whole wheat flour and whole wheat products.

However, a considerable number of questions remain to be addressed. For example, in situ linkages between phytochemicals and major wheat components (starch, protein, and cell wall polysaccharides) are poorly understood. Changes in phytochemicals during long-term storage are barely investigated. Even in areas that have been extensively reported such as extraction and characterization, there are limitations in methods that lead to inconsistent results and confusing data interpretations. In particular, the errors and misinterpretation of in vitro assays for the analysis of total phenolics, total flavonoids, and antioxidant activities are widely noted. It was common for results from different studies on the same topic to be incomparable due to different experimental conditions and laboratory methods. A lack of understanding of the chemistry of phytochemicals and of in vitro methods likely caused some of these problems. Although several reviews have summarized recent studies (Gupta et al., 2021; Liu et al., 2020; Luthria et al., 2015), it is equally important to realize the limitations of current results. Therefore, besides presenting representative results from recent years, this review strives to underline the limitations of current studies and provide possible resolutions as well as future research directions.

This review covers the key aspects in wheat phytochemical research including (1) the fundamental chemistry, distribution, and occurrence of wheat phytochemicals that are essential but not discussed in detail in previous reviews; (2) different extraction protocols of wheat phytochemicals and in vitro antioxidant assays that sometimes cause difficulty in data interpretation; (3) effects of genotypes (G), field management (M), and environments (E) including those of increasing popularity such as ancient grains and organic farming systems; (4) effects of grain and food processing including milling, seed germination, fermentation, enzymatic treatment, thermal treatment, and other processes; and (5) phytochemicals in the human digestive system and their health benefits (Figure 1). By covering wheat phytochemical from farm to fork, this review article is intended to serve as a useful reference for both expert and nonexpert readers.

2 | CHEMISTRY, EXTRACTION, AND OCCURRENCE OF WHEAT PHYTOCHEMICALS

2.1 | Phenolic acids

Phenolic acid, consisting of a phenolic ring and an organic carboxylic acid functional group, is among the most abundant phytochemicals in wheat. There are two major groups of phenolic acids: derivatives of hydroxybenzoic acids and derivatives of hydroxycinnamic acids. The most common phenolic acids found in whole wheat flour include 4-hydroxybenzoic acid, caffeic acid, vanillic acid, syringic acid, *para*-coumaric acid, *trans*-ferulic acid (FA), sinapic acid, and *cis*-FA. *Trans*-FA is the predominant phenolic acid in wheat, accounting for over 90% of the total phenolic acids (Adom et al., 2003). Phenolic acids are typically defined according to extraction protocols and exist in several forms: soluble-free, soluble-conjugated, and insoluble-bound (Moore et al., 2005). Soluble-free phenolic acids are extracted using organic solvents such as 80% aqueous ethanol (v/v) or methanol/acetone/water (7:7:6, v/v/v). Soluble-conjugated phenolic acids are further released by alkaline hydrolysis of the soluble extraction. Insoluble-bound phenolic acids are released by alkaline treatment

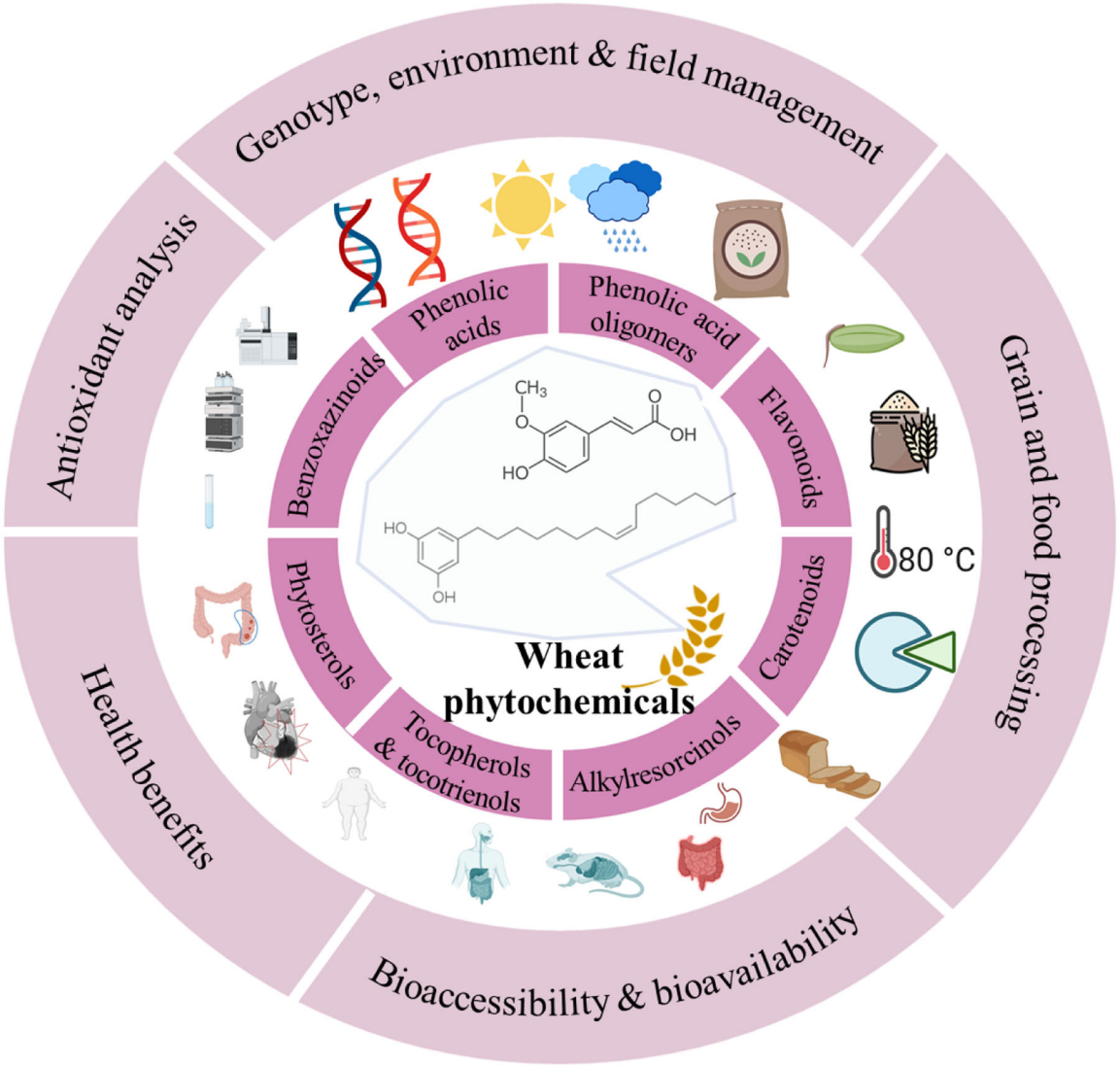


FIGURE 1 Overview of wheat phytochemicals: Composition, genetic diversity, processing effect, bioavailability, and health benefits

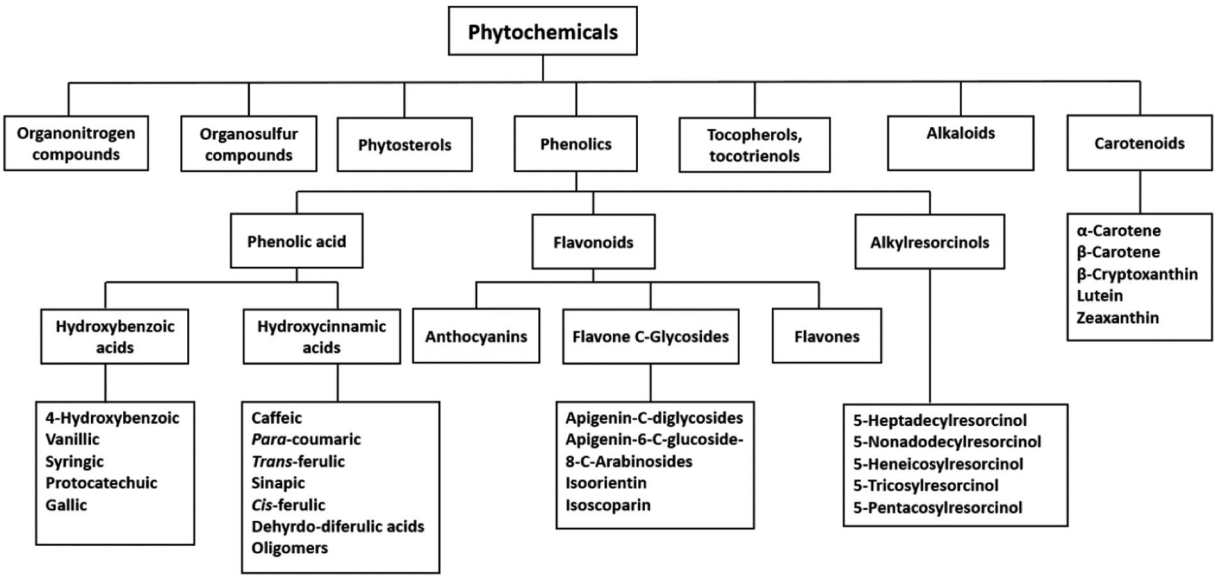


FIGURE 2 Classification of wheat phytochemicals

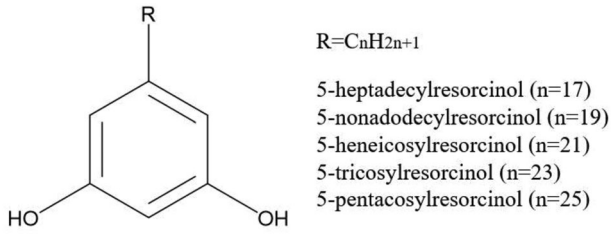


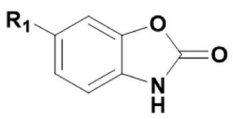
FIGURE 3 Structure of the common alkylresorcinols (ARs) in whole grains

of the residue after extraction of the soluble-free and soluble-conjugated fractions. Most (>90%) phenolic acids are present in the insoluble-bound form. The phenolic acid composition of whole wheat has been extensively reported (Li et al., 2008; Liu et al., 2020; Luthria et al., 2015) and is tabulated in Table 1. Unless specifically indicated, the soluble-free and soluble-conjugated phenolic acids are combined and referred to as soluble phenolic acids in this review, since the soluble-free phenolic acids account for less than 1% of total soluble phenolic acids.

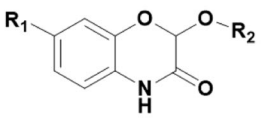
Vaidyanathan and Bunzel (2012) proposed classifying cereal product phenolic acids into free phenolic acids, phenolic acid esters linked to mono- and/or oligosaccharides, esters linked to soluble polysaccharides, and esters linked to insoluble polysaccharides. This classification method provides detailed information on the chemical structure and properties of phenolic acids but does not account for their extraction. Some recent studies did not differentiate various forms of phenolic acids and directly performed alkaline hydrolysis in the extraction and analysis of total esterified phenolic acids (Lu et al., 2014; Ma et al., 2015; Tian, Chen, Gui, et al., 2021; Tian, Chen, Tilley, et al., 2021). Lu et al. (2014) found that such a protocol generated more FA than the sum of soluble and insoluble FA extracted by the conventional method. It is possible that some phytochemicals are resistant to alkaline treatments and therefore are not released from the matrix. A possible solution is to use enzyme-assisted extraction. As several recent studies show, the extractability of phytochemicals is increased using simulated digestion compared to chemical extraction (Danesi et al., 2020; Tian, Hu, et al., 2021).

2.2 | Phenolic acid oligomers

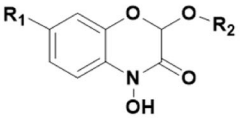
Phenolic acids exist in monomeric and oligomeric forms (Bunzel, 2010). Among the oligomers, diferulic acid (DFA) (i.e., dimers of FA) has been isolated, identified, and (semi)-quantified in studies (Dobberstein & Bunzel, 2010; Gong, Gao, et al., 2019; Tian, Chen, Tilley, et al., 2021). DFAs can be extracted along with other monomeric phenolic acids under the same conditions. Like monomeric phenolic acids, some DFAs exist in the soluble form, whereas the majority exist in the insoluble fractions (Bunzel et al., 2001). Common DFA isomers include 8-8



R1	Compound
H	BOA
OCH_3	MOBA



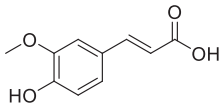
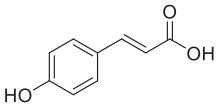
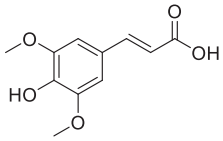
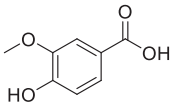
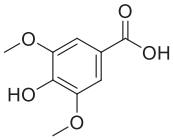
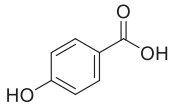
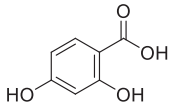
R1	R2	Compound
H	H	HBOA
OCH_3	H	HMBOA
H	Glc	HBOA-Glc
OCH_3	Glc	HMBOA-Glc
H	Glc-Hex	HBOA-Glc-Hex



R1	R2	Compound
H	H	DIBOA
OCH_3	H	DIMBOA
H	Glc	DIBOA-Glc
OCH_3	Glc	DIMBOA-Glc
H	Glc-Hex	DIBOA-Glc-Hex

FIGURE 4 Structure of the common benzoxazinoids (BXs) in whole grains. BOA, benzoxazolin-2-one; MBOA, 6-methoxy-benzoxazolin-2-one; HBOA, 2-hydroxy-1,4-benzoxazin-3-one; HMBOA, 2-hydroxy-7-methoxy-1,4-benzoxazin-3-one; HBOA-Glc, 2-β-D-glucopyranosyloxy-1,4-benzoxazin-3-one; HMBOA-Glc, 2-β-D-glucopyranosyloxy-7-methoxy-1,4-benzoxazin-3-one; HBOA-Glc-Hex, dihexose derivative of HBOA; DIBOA, 2,4-dihydroxy-1,4-benzoxazin-3-one; DIMBOA, 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one; DIBOA-Glc, 2-β-D-glucopyranosyloxy-4-hydroxy-1,4-benzoxazin-3-one; DIMBOA-Glc, 2-β-D-glucopyranosyloxy-4-hydroxy-7-methoxy-1,4-benzoxazin-3-one; DIBOA-Glc-Hex, dihexose derivative of DIBOA

TABLE 1 Composition of whole wheat phenolic acid

Name	Structure	Soluble (μg/g flour)	Insoluble (μg/g flour)
Hydroxycinnamic acids			
Trans-ferulic acid		9.4-70.0	162.0 to 721.0
Para-coumaric acid		1.7 to 12.1	2.9 to 19.1
Sinapic acid		19.1 to 128.0	13.6 to 36.6
Hydroxybenzoic acids			
Vanillic acid		7.0 to 24.5	1.7 to 9.0
Syringic acid		3.8 to 22.2	1.0 to 13.4
4-Hydroxybenzoic acid		2.0 to 11.1	0.2 to 8.6
2,4-Hydroxybenzoic acid		7.6 to 116	0 to 215.0

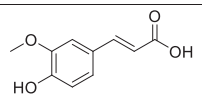
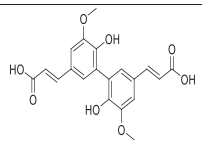
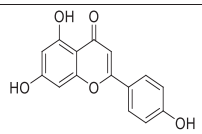
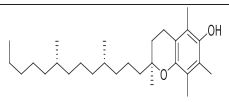
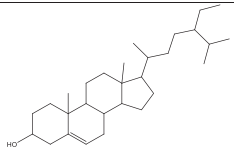
Note: Data taken from Li et al. (2008) and Liu et al. (2020).

DFA, 8-5 DFA, 5-5 DFA, 8-O-4′ DFA, and 8-5 benzofuran DFA. However, analytical standards of DFA isomers are not yet commercially available, and mass spectroscopy is generally required for the identification of DFA isomers. Currently, the lack of analytical standards limits the qualitative analysis of DFAs. Although DFA isomers can be isolated from cereal bran or synthesized in the laboratory, commercially available analytical standards at a reasonable price would significantly advance research. The establishment of a standard DFA quantification method is critical for the understanding of the chemistry, occurrence, and processing effects of FA since processing may induce either dimerization or de-dimerization.

2.3 | Flavonoids

Flavonoids possess a 15-carbon skeleton consisting of two benzene rings and a heterocyclic ring (i.e., C6–C3–C6 structure). They are divided into six different classes based on the C6–C3–C6 skeletons: anthocyanidins, chalcones, flavones, flavonols, flavanones, and isoflavones (Panche et al., 2016). Like phenolic acids, flavonoids in whole wheat exist in soluble and insoluble forms. They are usually extracted simultaneously with phenolic acids, and literature generally treats this process as the "extraction of phenolics" (Adom et al., 2003; Okarter et al., 2010). Qualitative analysis of wheat flavonoids is

TABLE 2 Overview of phytochemicals in whole wheat

Phytochemical	Example	Extraction	Analytical methods	Concentration (μg/ g whole flour)	Potential health benefits	Possible delivery mechanism
Phenolic acids		Soluble fraction by various organic solvents; insoluble fraction released by alkaline hydrolysis	HPLC/UPLC; identified and quantified by analytical standards	See Table 1	Antioxidant; anti-inflammatory; anti-cancer; reduced risk of CVDs; diabetes management	Passive diffusion
Oligomer of hydroxycinnamic acids	 5-5 DFA	Together with phenolic acids as soluble and insoluble fractions	HPLC/UPLC; identified by mass spectroscopy; semi-quantitative estimation	Lack analytical standards	Antioxidant	Unknown
Flavonoids	 Apigenin	Together with phenolic acids as soluble and insoluble fractions	HPLC/UPLC; identified by mass spectroscopy; measured by aluminum assay as total flavonoids	Lack analytical standards	Antioxidant; anti-inflammatory; anti-cancer; reduced risk of CVDs; diabetes management	Passive diffusion; via sodium-glucose transport proteins (for flavonoid-glucosides); via lactase phlorizin hydrolase
Tocopherols and tocotrienols	 α -Tocopherol	Organic solvents; saponification extraction using KOH	HPLC/UPLC; identified and quantified by analytical standards	Total tocopherols and tocotrienols range from 27.6 to 79.7	Antioxidant; anti-inflammatory	Mainly through passive diffusion; mediated by class B type 1 (SRB1), a cluster of determinant 36 (CD36), and Niemann–Pick C1-like 1 protein (NPC1L1)
Carotenoid	 Lutein	Organic solvents methanol/tetrahydrofuran (1:1, v/v) and ethanol/acetone/hexane mixture (1:1:2, v/v/v)	HPLC/UPLC; identified and quantified by standards	Lutein 0.24 to 2.11; zeaxanthin 0.08 to 0.53; β-carotene 0.10 to 0.21	Antioxidant; pro-vitamin A (β-carotene and β-cryptoxanthin); vision support (lutein and zeaxanthin)	Mainly through passive diffusion; mediated by SRB1, CD36, and NPC1L1
Alkylresorcinol	 5-Heneicosylresorcinol (AR21)	Organic solvents: acetone and ethyl acetate; supercritical CO_2 extraction	HPLC/UPLC, GC; identified and quantified by standards	Total alkylresorcinols range from 194 to 741	Anti-inflammatory; anti-cancer; biomarkers of whole grain intake	Passive diffusion and to some extent mediated by SRB1
Phytosterol	 Sitosterol	Alkaline and acid hydrolysis for free, esterified, and glycoside forms	GC/GC-MS; identified and quantified by standards	Total phytosterols range from 670 to 1187	Reduce low-density lipoprotein (LDL) cholesterol; anti-cancer	Via the sterol transporter NPC1L1

Note: Information taken from Adom et al. (2003), Andersson et al. (2008), Lampi et al. (2008); Moore et al. (2005), Nurmi et al. (2008), and Okarter et al. (2010), and sources cited in Sections 5 and 6 of this review.

limited due to their relatively low concentrations and a lack of analytical standards. Past studies have mainly focused on identification and structural characterization. An analysis of anthocyanins in purple pericarp wheat identified 13 anthocyanins with cyanidin 3-glucoside being predominant (Hosseinian et al., 2008). Geng et al. (2016) identified 72 flavone C-glycosyl derivatives in wheat germs using ultrahigh-performance liquid chromatography–photodiode array detection–electrospray ionization/high-resolution mass spectrometry (UPLC–PDA–ESI/HRMS) and mass defect filtering protocols. Wang et al. (2020) identified 174 flavonoids compounds in five colored wheat grains using the ultrahigh-performance liquid chromatography–electrospray ionization-uadrupole-linear ion trap/tandem mass spectrometry (UPLC–ESI–Q TRAP–MS/MS) system. More often, the flavonoid contents of whole wheat are determined by in vitro colorimetric assays and expressed as the catechin equivalence (CE) or quercetin equivalence (QE) per gram of flour. Although there are minor variations among different methods (Adom et al., 2003; Leoncini et al., 2012; Tian & Li, 2018), the key principle is to quantify total flavonoid content (TFC) according to UV absorbance of the aluminum–flavonoid complex. Leoncini et al. (2012) reported that soluble TFC of six wheat genotypes ranged from 0.09 to 0.32 mg CE/g flour and insoluble TFC ranged from 0.10 to 0.35 mg CE/g flour. Similarly, Tian and Li (2018) measured the flavonoid concentrations of 12 hard red winter wheat genotypes and found that soluble TFC ranged from 0.03 to 0.06 mg CE/g flour and insoluble TFC ranged from 0.33 to 0.73 mg CE/g flour. However, this TFC assay likely overestimates the concentration of flavonoid compounds due to its nonspecificity (Papoti et al., 2011). This assessment was supported by the fact that the reported TFC range (from 0.1 to 0.35 mg/g flour) was comparable to that of insoluble FA (Leoncini et al., 2012), which is obviously overestimated. In summary, this aluminum assay for "total flavonoid content" is potentially erroneous and thus not recommended for future use in the evaluation of cereal extracts. More specific and robust quantification methods need to be established.

2.4 | Carotenoids

Carotenoids are mostly C40 terpenoids, and over 750 carotenoids have been identified in nature (Nisar et al., 2015). In recent years, carotenoids have been extensively studied as provitamin-A and antioxidants in the human diet. Lutein, zeaxanthin, β-cryptoxanthin, and β-carotene are common carotenoids found in whole wheat flour. Carotenoids can be extracted by organic solvents or a mixture of several organic solvents such as methanol/tetrahydrofuran (1:1, v/v) or ethanol/acetone/hexane (1:1:2, v/v/v) mixtures (Lv et al., 2013; Paznocht et al., 2018). BHT (butylated hydroxytoluene) and THBQ (tert-butylhydroquinone) can be used at 0.1% (w/v) during the extraction process to protect against oxidation (Mellado-Ortega & Hornero-Méndez, 2017; Whent et al., 2012). Carotenoids can also be extracted via supercritical fluid extraction as summarized in a previous review (Luthria et al., 2015).

Adom et al. (2003) analyzed the carotenoids of 11 wheat genotypes. Lutein concentration ranged from 0.24 to 1.43 μg/g grain; zeaxanthin concentration ranged from 0.08 to 0.27 μg/g grain; and β-cryptoxanthin concentration ranged from 0.01 to 0.13 μg/g grain. Moore et al. (2005) analyzed carotenoids in 12 soft wheat genotypes and found that concentration ranges for β-carotene, zeaxanthin, and lutein were 0.10−0.21, 0.20−0.39, and 0.82−1.14 μg/g of grain, respectively. Okarter et al. (2010) reported that lutein concentration ranged from 0.67 to 2.11 μg/g grain, zeaxanthin concentration ranged from 0.25 to 0.53 μg/g grain, and β-cryptoxanthin concentration ranged from 0.12 to 0.20 μg/g grain. Carotenoids in ester-linked forms with fatty acids (such as palmitic, stearic, oleic, and linolenic acids) were reported more than 50 years ago (Lepage & Sims, 1968). Studies in recent years confirmed that lutein exists in both free and esterified forms in some wheat genotypes and other cereal grains (Paznocht et al., 2018; Requena-Ramírez et al., 2021). According to a recent report, lutein esters were detected in only 11 of 156 durum wheat genotypes (Requena-Ramírez et al., 2021), though they were more common in bread wheat and spelt wheat genotypes (Ziegler et al., 2015). Transition from free lutein to ester-linked lutein during long-term storage was also reported (Mellado-Ortega & Hornero-Méndez, 2017). It is suspected that lutein in ester or diester forms is more stable during food processing (Ahmad et al., 2013), but further studies are needed for a thorough understanding of the properties of carotenoid esters, which might have potential for biofortification.

2.5 | Alkylresorcinols

Alkylresorcinols (ARs), also known as resorcinol lipids, are phenolic lipids composed of odd-numbered aliphatic chains and resorcinol-type phenolic rings. More than 100 types of ARs in plants and microorganisms have been identified in previous studies; however, whole grain barley, wheat, and rye were reported to be the primary food sources for ARs (Landberg et al., 2014). Therefore, ARs and their metabolites are potential biomarkers for tracking the consumption of whole grain products (McKeown et al., 2016). A clinical study found that plasma AR

concentrations were positively correlated with whole grain consumption (Ross et al., 2012). ARs in wheat grain usually contain a saturated aliphatic side chain with 17, 19, 21, 23, or 25 carbons (Figure 3). ARs with unsaturated side chains have also been identified (Zhu et al., 2011). ARs can be extracted by organic solvents such as methanol, acetone, and ethyl acetate, as well as via a supercritical CO_2 method (Gunenc et al., 2015). Analytical standards for ARs are commercially available but very expensive, which to some extent limits research progress in this field. Andersson et al. (2008) reported that concentrations of total ARs in 175 wheat genotypes ranged from 191 to 741 μg/g flour. Thus, the concentration of ARs is comparable to that of *trans*-FA in wheat. Future studies should consider ARs one of the most important phytochemicals in whole wheat, and more studies on ARs from farm to fork should be carried out. For example, the effect of baking on ARs, especially those with unsaturated side chains, is worth further investigation. Moreover, the total AR content was more heritable (63%) than that of phenolic acids (28%) (Shewry et al., 2012). It is therefore of interest to develop new wheat genotypes with enhanced total AR contents.

2.6 | Tocopherols and tocotrienols

There are eight common, naturally occurring isomers of vitamin E (alpha-, beta-, gamma-, and delta-tocopherols; alpha-, beta-, gamma-, and delta-tocotrienols). Tocopherols have saturated side chains, and tocotrienols have unsaturated side chains. Alpha-tocopherol is the major form of vitamin E in animal products, whereas cereal grains are a rich source of tocotrienols. There are three common protocols for extracting vitamin E from cereals: organic extraction, extraction without saponification, and extraction with saponification (Panfili et al., 2003). Direct organic extraction employs solvents such as methanol and methanol/tetrahydrofuran (1:1, v/v) (Moore et al., 2005). For extraction with saponification, vitamin E is extracted from wheat flour using 95% ethanol solution with sodium chloride, pyrogallol, ascorbic acid, and potassium hydroxide solution (Okarter et al., 2010). Extraction without saponification works similarly except that the potassium hydroxide solution is replaced with distilled water. Panfili et al. (2003) found that extraction with saponification achieved a higher yield (44.1 μg/g) than organic extraction (29.8 μg/g) or extraction without saponification (35.1 μg/g). This demonstrated that tocopherols and tocotrienols also exist in ester forms or as compounds bound to the matrix. These latter compounds are analogs of soluble-conjugated and insoluble-bound phenolic acids. Currently, few studies have differentiated different forms of vitamin E in whole grains. As demonstrated for phenolic acids, different forms of vitamin E in whole wheat may have different stabilities during storage and processing. It is therefore important to investigate the effects of food processing on natural vitamin E isomers and their esters.

2.7 | Phytosterols

Phytosterols have chemical structures similar to that of cholesterol except for having an extra methyl or ethyl group (Zhu & Sang, 2017). Sitosterol is the predominant phytosterol in whole wheat, accounting for over 50% of total sterols. Other common phytosterols are campesterol, sitostanol, and campestanol (Nurmi et al., 2008). Previously, phytosterols were believed to exist in free, ester, glycoside, and acylated glycoside forms (Toivo et al., 2000). Further GC–MS characterization indicated that sterols also exist as sterol ferulates, steroid hydrocarbons, and steroid ketones (Prinsen et al., 2014). A general extraction protocol employs step-wise acid and alkaline hydrolysis to release sterols from their glycoside and ester conjugates. Nurmi et al. (2008) reported that the concentration of total phytosterols in whole wheat flour ranged from 670 to 1187 μg/g among 175 wheat genotypes. The concentration of total phytosterols is comparable to that of phenolic acids, which is generally believed to be the most predominant phytochemical in whole wheat. The cholesterol-lowering effect of phytosterols has been widely recognized (Plat & Mensink, 2005). However, their overall health benefits are much less studied than that of phenolic acids. Additional studies on phytosterols such as their stability during food processing are necessary to fully understand their potential health benefits in whole grain products.

2.8 | Benzoxazinoids

Previously, BXs were believed to exist mainly in the roots and shorts of some cereals as an important part of the plants' defense system (Sicker et al., 2000). In recent years, studies found that BXs were also present in mature grains of wheat and rye (Villagrasa et al., 2006). The potential health benefits of BXs include antioxidant, anti-inflammatory, and anticancer activities and support of the central nervous system (Adhikari et al., 2015). BXs are generally divided into three groups according to their structures: benzoxazolinones, lactams, and hydroxamic acids (Figure 4). Tanwir et al. (2013) found that dihexose of 2,4-dihydroxy-1,4-benzoxazin-3-one (DIBOA-Glc-Hex) was the predominant form of BXs. Their results showed that wheat germ contained the highest DIBOA-Glc-Hex concentration (95 μg/g) followed by coarse bran (44 μg/g), fine bran (28 μg/g), whole flour (3.3 μg/g), and refined

flour (0.6 μg/g). That DIBOA-Glc-Hex is the predominant form of BX was supported by several studies (Dihm et al., 2017; Savolainen et al., 2015). However, Kowalska and Jędrejek (2020) found that glucoside of 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (DIMBOA-Glc) was the predominant form of BXs. They also reported that the total BXs of 26 wheat varieties ranged from 31 to 859 μg/g whole flour. This reported range was consistent with the result from Dihm et al.(2017) but much higher than the result from Tanwir et al. (2013). In summary, current studies showed some contradictory results about the predominant form and total content of BXs in wheat grains. This may be due to the lack of high-purity and commercially available standards of BX-glucosides. Further, the above studies used mass spectroscopy for quantification. Quantification of plant metabolites using mass spectroscopy is very complicated and challenging (Alseekh et al., 2021). If the BX concentration could reach the level of several hundred microgram per gram (μg/g) whole flour as reported by some studies, then UV or photodiode array (PDA) detectors may more easily and reliably quantify major BXs. Future studies are necessary to confirm the predominant form of BXs as well as the effects of wheat genotypes and environment on total BX contents.

2.9 | In vitro antioxidant assays

An antioxidant is "a substance that, when present at a low concentration compared with that of an oxidizable substrate in the medium, inhibits oxidation of the substrate" (Halliwell & Gutteridge, 2015). Wheat phytochemicals including phenolic acids, flavonoids, carotenoids, and others that exhibit antioxidative capacities are natural antioxidants. There are three major functioning mechanisms for antioxidants: hydrogen atom transfer (HAT), single electron transfer (SET), and transition metal chelation. In both HAT and SET, the antioxidant forms a "stale" radical that is much less reactive. For example, FA, with its phenolic ring and side chain conjugation, can form a resonance-stabilized phenoxy radical that accounts for its strong antioxidant potential (Graf, 1992). Amić et al. (2020) found that the phenoxyl radical in FA could undergo coupling with another free radical and dimerization to form DFAs and H-atom donation (Figure 5). The dimerization of FA in a ferulic-acid-free radical reaction system was confirmed by a recent report (Yang et al., 2021).

Many in vitro assays have been developed for the evaluation of antioxidant potential. Examples of these assays include the cupric ion reducing antioxidant capacity (CUPRAC), ferric reducing ability of plasma (FRAP), 1,1-diphenyl-2-picrylhydrazyl (DPPH), 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) free radical scavenging, oxygen radical absorbance capacity (ORAC), and inhibition of lipoperoxidation assays (Shahidi & Zhong, 2015). Folin–Ciocalteu reagent is often used to determine "total phenolic content" (TPC); however, reduction of the Folin–Ciocalteu reagent happens mainly through the SET mechanism. Therefore, phenolics are the major contributors to the observed antioxidant activity of tested whole wheat extracts. One major drawback of these popular methods is that they are all extraction dependent. To overcome this problem, a direct measurement of antioxidant activity without sample extraction based on ABTS, DPPH, and ORAC assays was proposed (Henrion et al., 2018). However, radicals in these assays are not biologically relevant, and the mechanisms of the reactions are not clear (Apak et al., 2013). Due to these significant drawbacks, a previous review recommended the discontinuation of ABTS/DPPH assays and a significant revision of the ORAC assay (Schaich et al., 2015). The U.S. Department of Agriculture (USDA) launched an online ORAC database in 2010 but removed it in 2012 "due to mounting evidence that the values indicating antioxidant capacity have no relevance to the effects of specific bioactive compounds, including polyphenols on human health." The *Journal of Food Composition and Analysis* has not accepted papers that employ in vitro antioxidant and total phenolic assays since 2017 (Harnly, 2017), and *Food Chemistry* has not accepted papers with only in vitro results since 2018 (Granato et al., 2018). Generally speaking, in vitro assays are easier to perform and remain suitable for screening and quality control purposes, but they are sometimes misused and/or inappropriately interpreted. The concepts of "oxidative stress" and "free radical damage" are generally accepted by the scientific community, but antioxidant activity measured by in vitro assays is not relevant to address the redox balance in vivo under most conditions. Future studies are needed to analyze specific compounds and limit the use of nonspecific "total" methods. Meanwhile, it should also be emphasized that phytochemicals in whole wheat and other food sources may function in vivo through mechanisms other than antioxidation.

3 | EFFECTS OF GENOTYPES, ENVIRONMENTS, AND FIELD MANAGEMENT ON WHEAT PHYTOCHEMICALS

Wheat grain phytochemical profiles are affected by genotypes (G), environments (E), and field management (M). The effect of genetic variations on phytochemical profiles has been widely recognized. Li et al. (2008) analyzed the phenolic acid composition of 175 wheat genotypes grown

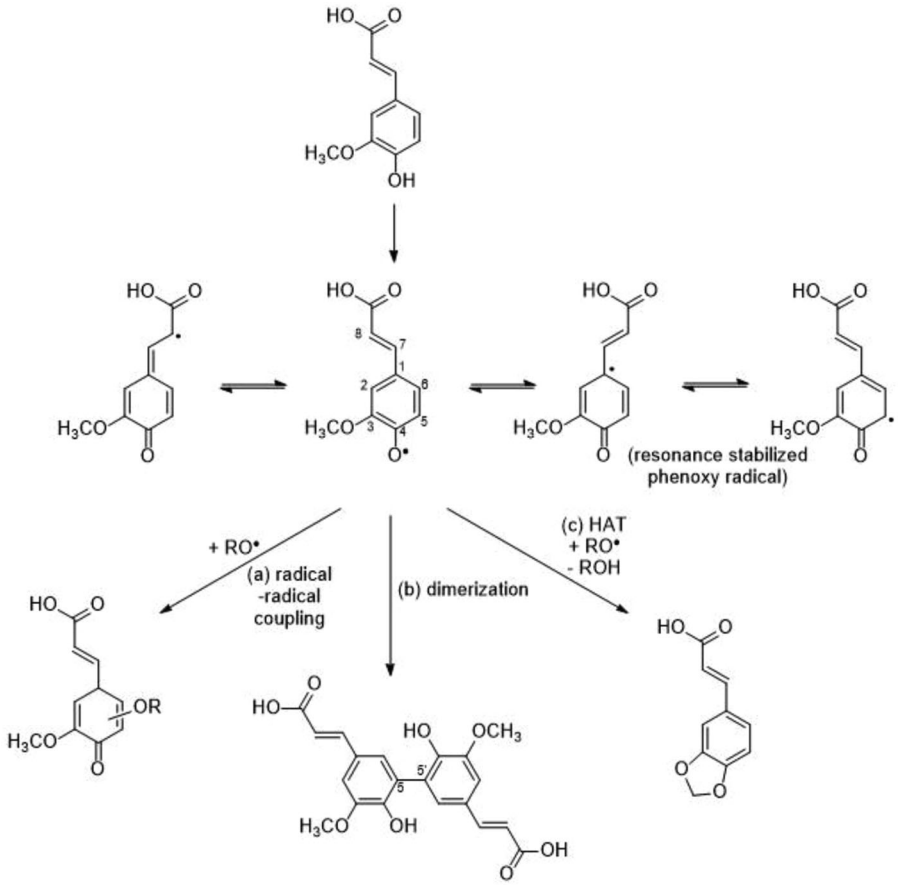


FIGURE 5 Proposed antioxidative mechanisms of ferulic acid according to Graf (1992) and Amić et al. (2020)

at the same location in 2005. The highest concentration of total phenolic acids was 1171 μg/g with an average level of 658 μg/g. Winter wheats displayed a range of >3.5-fold, and spelt genotypes displayed the narrowest (1.9-fold) range in total phenolic acid concentration. Ma et al. (2014) reported that TPC of 187 Chinese common wheat genotypes grown in the same environment ranged from 492 to 1313 μmol GAE/100 g. In addition to TPC and phenolic acids, significant genetic variations in the contents of ARs (Andersson et al., 2008), tocopherols and tocotrienols (Lampi et al., 2008), and phytosterols (Nurmi et al., 2008) were also demonstrated in the EU Framework Programme 6 HEALTHGRAIN project. In recent years, ancient wheat genotypes are becoming popular as a potential source for functional foods. Gotti et al. (2018) analyzed phenolic acid concentrations of five modern wheat genotypes and five ancient wheat genotypes. The ancient genotypes contained significantly higher concentrations of phenolic acids. Loreto et al. (2018) similarly analyzed phenolics in 13 ancient wheat genotypes and nine modern wheat genotypes. Again, the ancient genotypes contained higher concentrations of phenolic acids than modern genotypes. However, these studies are not comprehensive due to the limited number of genotypes involved. More studies are needed to confirm if ancient wheat genotypes contain higher concentrations of bioactive components (Shewry & Hey, 2015).

The content and profile of phenolic acids and other phytochemicals are also influenced by environment (E), field management (M), and interaction effects (G × E, G × M, and G × E × M). Fernandez-Orozco et al. (2010) grew 26 wheat genotypes in Hungary for three consecutive years and then in three additional countries in the final year. Analysis of phenolic acids indicated that locations and years significantly influenced the concentration, especially the soluble forms of phenolic acids. However, the phenolic acid concentrations of some genotypes were more inconsistent in different environments, which suggested the interaction between genotypes and environments. Similar conclusions were reported by several other studies (Martini et al., 2014; Silvestro et al., 2017). Lu et al. (2015) analyzed phytochemical profiles of 10 wheat genotypes grown at four locations with results showing significant effects of G, E, and G × E. Environmental factors had a stronger effect than genotype or G × E interaction on TPC, ABTS, and DPPH antioxidant activities and soluble phenolic acids. Pu et al. (2019) analyzed TPC of 28 diverse wheat genotypes grown at seven locations for

2 years. Their results suggested that higher temperatures and longer hours of sunshine were the major driving force for enhanced TPC.

Effects of farm management, together with effects of genotypes and environments, were reported by previous studies. Fertilizer application has been the most studied management factor. Ma et al. (2015) found that irrigation level, nitrogen fertilizer application, and their interaction had a significant effect on the TPC, antioxidant activity, and phenolic acid composition of wheat grains. Similarly, Tian, Wilson, et al. (2021) found that increased nitrogen fertilization led to increased accumulation of *trans*-FA and the effect interacted with genotypes and sulfur fertilization. By contrast, Stumpf et al. (2019) found that higher amount of nitrogen fertilization led to decreased concentrations of soluble FA and did not affect insoluble FA and TPC. The effect of organic farming has also been studied. Zuchowski et al. (2011) studied eight wheat genotypes and found that wheat grains from organic farming systems contained higher TPC, FA, and *para*-coumaric acid. Similarly, Pandino et al. (2020) studied 10 durum wheat genotypes and showed that organic farming systems increased wheat extracts' soluble TPC and antioxidant activity compared to conventional farming systems. By contrast, Fares et al. (2019) tested nine genotypes for 2 years and found that organic farming did not affect antioxidant activity or phenolic acid composition. More studies are needed to understand if organic farming increases the accumulation of phytochemicals in wheat grain.

In summary, genotypes, environments, management factors, and their interactions can significantly affect wheat grain phytochemical profiles (Table 3). There are some inconsistent results that are possibly due to different experimental designs, data processing, and forms of phenolics and the limitation of total phenolic/antioxidant assays as discussed in Section 2. Furthermore, for fertilizer studies, different forms of a fertilizer (e.g., N fertilizer applied as $(NH_4)_2SO_4$, $NaNO_3$, NH_4NO_3, urea, or organic matter) may have different effects that need to be further investigated. Residue fertilization levels in soil may also play important interactive roles with the applied fertilizers. Therefore, future studies on the effect of fertilizer application are advised to consider the forms of fertilizers and residue fertilizers in the soil. Another drawback of many studies is the lack of detail regarding the term "environment." Wheat genotypes growing in different years and locations are subjected to different temperatures, precipitation, sunlight, pests, and diseases. In most studies, all of these factors were treated as a single fixed effect ("environment") for statistical analysis. Environmental conditions should be dissected in greater detail in future studies. In addition, the interactive effect of G × E × M will be important to study for future wheat breeding and production programs. Any trait (e.g., high concentrations of a phytochemical) must have high heritability across environments for successful breeding outcomes. Shewry et al. (2012) reported that the heritability of tocols (tocopherols and tocotrienols), phytosterols, and ARs was 76%, 57%, and 63%, respectively, whereas the heritability of phenolic acids was only 28%. This suggests that the concentration of phenolic acids is more likely to be affected by environment and management, whereas the concentrations of tocols, phytosterols, and ARs are more dependent on wheat genotype.

4 | EFFECTS OF GRAIN AND FOOD PROCESSING ON WHEAT PHYTOCHEMICALS

The effects of various grain and food processing procedures on wheat phytochemicals have been well studied in recent years. Many processing techniques were investigated as means to improve phytochemical bioaccessibility, bioavailability, and antioxidant activity. Here, we discuss the effects of common processing procedures and provide some representative results (Table 4). Since there is no standard protocol for "complete" extraction of phytochemicals, the various studies measure changes in "extractable" phytochemicals in relation to processing. Processing can modify the chemical structure of phytochemical molecules or simply increase/decrease the extractability of phytochemicals via physical mechanisms. Furthermore, the nonspecificity of in vitro assays means that other components generated during processing, such as bioactive peptides and polysaccharides, might also contribute to changes in antioxidant capacity, especially the soluble fraction. In short, care must be taken when interpreting results regarding the effects of processing procedures. Since the ultimate purpose is to increase the content of bioavailable phytochemicals, replacing chemical extraction with simulated digestion methods could help to clarify data interpretation in future studies.

4.1 | Seed germination

Germination is a physiological process where a cascade of biochemical changes occurs to facilitate the development of a seedling (Poudel et al., 2019). Germination can affect the nutraceutical value of whole grains. Žilić et al. (2014) found that TPC, free radical scavenging activities, and concentrations of *trans*-FA, *para*-coumaric acid, and caffeic acid increased after 5 days of germination. Kim et al. (2018) reported that phenolic acids, γ-aminobutyric acid (GABA), and antioxidant activities increased with increasing

TABLE 3 Effects of genotypes, environments, and field management on wheat phytochemicals

Factors	Experiment designs	Results	References
Genotypes	175 wheat genotypes in the HEALTHGRAIN Diversity Screen	Phenolic acids ranged from 449 to 1171 μg/g; total alkylresorcinols ranged from 194 to 741 μg/g; total tocopherols and tocotrienols dm ranged from 27.6 to 79.7 μg/g; total sterols ranged from 670 to 959 μg/g	Andersson et al., 2008; Lampi et al., 2008; Li et al., 2008; Nurmi et al., 2008
Genotypes	184 common Chinese genotypes	TPC ranged from 492 to 1313 μmol gallic acid equivalence (GAE)/100 g	Ma et al., 2014
Genotypes	Five ancient and five modern wheats grown under the same conditions	Ancient wheats contained higher concentrations of phenolic acids	Gotti et al., 2018
Genotypes	13 ancient and nine modern genotypes	Ancient wheats contained higher concentrations of phenolic acids	Loreto et al., 2018
Genotypes (G) and environments (E): different locations and growth year	Three durum wheats grown at several locations for 2 years	Soluble phenolics were primarily affected by E; insoluble phenolics were primarily affected by G	Martini et al., 2014
Genotypes (G) and environments (E): different locations and growth year	Seven genotypes organically grown at three locations for 3 years	Soluble phenolics were primarily affected by E; insoluble phenolics were primarily affected by G	Silvestro et al., 2017
Genotypes (G) and environments (E): different locations	10 wheat genotypes in four locations	Total carotenoids were primarily affected by E (45.7%) and significantly correlated with low temperature and precipitation level; total tocopherols were primarily affected by G × E (71.6%)	Lu et al., 2015
Genotypes (G) and environments (E): drought and high temperature	Traditional and pigmented (yellow, blue, and purple) wheat genotypes	Blue aleurone genotypes contained less carotenoids than conventional bread wheat; purple pericarp genotypes had similar or more carotenoids than conventional bread wheat; drought and high temperature promoted carotenoids production	Paznocht et al., 2018

(Continues)

TABLE 3 (Continued)

Factors	Experiment designs	Results	References
Genotypes (G) and environments (E): different locations and growth year	28 diverse wheat genotypes at seven locations for 2 years	Higher temperatures and longer hours of sunshine enhanced TPC	Pu et al., 2019
Genotypes (G) and environments (E)	Four spring einkorn, four emmer, four spelt, and four common wheat genotypes cultivated under an organic cropping system in 2-year trials	TPC was in order of einkorn > emmer > common wheat > spelt; higher TPC in 2018, a very dry year	Zrcková et al., 2019
Management (M): different nitrogen fertilizer treatments	N0: no N fertilization; N75: 40 + 35 + 0 kg·N/ha; N150a: 80 + 70 + 0 kg·N/ha; N150b: 80 + 40 + 30 kg·N/ha; N195: 104 + 91 + 0 kg·N/ha; applied at tillering, culm elongation, and booting stages	Increased nitrogen rate decreased soluble ferulic acid but did not affect insoluble ferulic acid and TPC	Stumpf et al., 2019
Management (M): different cropping systems	10 durum wheat genotypes grown in organic and conventional cropping systems	Organic cropping system increased soluble TPC and antioxidant activity	Pandino et al., 2020
Management (M): different cropping systems	Three ancient genotypes and six modern genotypes in organic and conventional cropping systems for 2 years	Except for TPC, organic farming did not affect phenolic acid composition or antioxidant activity	Fares et al., 2019
Environments (E) and management (M)	Four N rates (0, 180, 240, and 300 kg/ha) combined with irrigation times (I_0: no irrigation; I_1: jointing time irrigation; I_2: jointing + flowering time irrigation)	Appropriate irrigation and N management improved in vitro antioxidant potential and concentrations of phenolic acids	Ma et al., 2015
Genotypes (G), environments (E), and management (M)	Four genotypes, three nitrogen levels, two sulfur levels, and 2-year experiments	Increased nitrogen fertilizer led to increased production of *trans*-ferulic acid; genotypes differed in response to sulfur application	Tian, Wilson, et al., 2021

TABLE 4 Effects of grain and food processing on wheat phytochemicals

Treatments	Phytochemicals	Results	References
Ultrafine grinding	Phenolic acids, flavonoids, and carotenoids	Increased extracted flavonoids and carotenoids; particle size influenced extraction rate	Brewer et al., 2014
Different particle size	Phenolic acid	Positive correlation between phenolic acid and particle size of milled fractions	Memon et al., 2020
Gelatinization	Total ester-linked phenolic acids	Microwave treatment gelatinized starch, resulting in decreased extraction yield	Lu & Luthria, 2016
Thermal processing	Soluble phenolic acids	Soluble ferulic acid +39.18%, vanillic acid +95.68%, apigenin–glucoside +71.96%, and *p*-coumaric acid +71.91%	Călinoiu & Vodnar, 2020
Hydrothermal and hot air drying	AR and soluble TPC	Improved AR extractability and changes in AR homologue composition; decreased soluble TPC	Ciccoritti et al., 2021
Autoclave treatment	Phenolic acid and flavonoid	Increased free ferulic acid from 6.41 to 24.13 mg/100 g bran and increased content of apigenin-6-C-arabinoside-8-C-hexoside	Rico et al., 2020
Steam flash explosion	Soluble ferulic acids, cellular antioxidant, and antiproliferative activity	Increased concentration of soluble ferulic acids; increased antioxidant activity	Chen et al., 2016
UV-B radiation	In vitro TPC, ABTS, and DPPH	Total phenolics, DPPH, and ABTS values (soluble + insoluble) significantly increased by 26.3%, 25.1%, and 12.0%, respectively	Chen et al., 2019
Ozone treatment	Soluble TPC, ABTS, and DPPH	No significant change	Alexandre et al., 2018
Germination (24, 48, and 72 h)	Phytic acid and γ-aminobutyric acid (GABA)	Decreased phytic acid and increased GABA from 24 to 72 h	Poudel et al., 2019
Germination (96 h)	Phenolic acids and γ-aminobutyric acid (GABA)	Increased concentrations of phenolic acids and GABA	Kim et al., 2018
Germination (<24 h)	Phenolic acids and in vitro antioxidant potential	Decreased soluble and insoluble phenolic acids; decreased TPC, ABTS, and DPPH values	Tian et al., 2019
Solid state fermentation	Soluble TPC and DPPH	Increased TPC and DPPH values	Zhai et al., 2015
Solid state yeast fermentation (0–6 days)	Soluble phenolic acids and flavonoids	Ferulic acid +56.6%, vanillic acid +259.3%, dihydroxybenzoic acids +161.2%, and apigenin-glucoside +15.3% (day 3)	Călinoiu et al., 2019

(Continues)

TABLE 4 (Continued)

Treatments	Phytochemicals	Results	References
Fermentation with 12 lactic acid bacterial strains	Phenolic acids and carotenoids	Two out of 12 strains had increased lutein content; changes of phenolic acid profiles depended on strains	Antognoni et al., 2019
Bread yeast fermentation	Soluble and insoluble phenolics	Increased soluble phenolic acid concentration	Tian, Chen, Tilley, et al., 2021
Sourdough fermentation	Soluble polyphenols and flavonoids	Increased soluble flavonoids and polyphenols	Saa et al., 2017
Sourdough fermentation	Nontargeted profiling	118 compounds with significantly increased concentrations and 69 compounds with significantly decreased concentrations	Koistinen et al., 2016
Enzymatic treatments by β-endoxylanase and α-arabinofuranosidase	Phenolic acids	Release of insoluble phenolic acids into soluble fractions	Xue et al., 2020
Enzymatic treatments by 13 commercial enzymes	Phenolic acids and in vitro antioxidant potential	Ultraflo XL released most phenolic acid from insoluble fraction to soluble fraction	Bautista-Expósito et al., 2020
Breadmaking	Phenolic acids; in vitro antioxidant potential	Increased soluble phenolics; decreased insoluble phenolics	Yu & Beta, 2015
Breadmaking	Phenolic acids	Significantly increased soluble phenolic acids; incorporation of phenolic acids into Maillard reaction products; some increase of insoluble phenolic acids	Tian, Chen, Tilley, et al., 2021
Bun-making	Carotenoids	Carotenoids degraded mostly due to dough preparation, not heat treatment; esterified carotenoids degraded to a similar extent as free carotenoids	Paznocht et al., 2019
Kernel puffing	Phenolic acids	Soluble phenolic acids increased; insoluble phenolic acids did not change	Hidalgo et al., 2016
Extrusion	In vitro TPC and DPPH assay	Optimized extrusion conditions increased TPC and DPPH values in wheat bran	Ramos-Enríquez et al., 2018
Puffing and extrusion	Carotenoids	Decreased concentration of total carotenoids; E- to Z-isomerization of lutein and zeaxanthin	Paznocht et al., 2021

germination time from 0 to 96 h. GABA concentration was the highest (39.98 mg/100 g grain) after 96 h of germination. The ORAC value was 1.97 times higher than that of the control after 96 h of germination. Similarly, Poudel et al. (2019) reported increased concentration of GABA after germination. Most studies agreed that longer times of germination increased the concentration of phytochemicals. In addition, another study found that shorter times (e.g., less than 24 h) decreased soluble TPC, radical activities, metal-chelating activities, and phenolic acid concentrations of wheat grains (Tian et al., 2019), which may be attributed to the activities of decarboxylase, esterase, and reductase enzymes. In summary, longer germination enhanced the nutraceutical values of wheat grains but at the expense of end-use properties (e.g., breadmaking and quality). Composite flours made from mixtures of germinated grain and sound grain in appropriate ratios may have the potential to produce acceptable end-use products with enhanced nutraceutical values.

4.2 | Milling

Milling is the process of grinding and fractionating wheat (and other grains) into flour and other products in preparation for further processing and food production. The distribution of phytochemicals in different milled fractions and their antioxidant activities have been thoroughly studied. Adom et al. (2005) evaluated phytochemicals and hydrophilic and lipophilic antioxidant activities of milled fractions (the endosperm and bran/germ) of three wheat genotypes. In whole wheat flour, the bran/germ fractions contributed 83% of the TPC, 79% of the TFC, 51% of the total lutein, 78% of the total zeaxanthin, 42% of the total β-cryptoxanthin, 85% of the total hydrophilic antioxidant activity, and 94% of the total lipophilic antioxidant activity. Spaggiari et al. (2020) confirmed that the concentration of phenolic compounds in bran is higher than that in other milled fractions. Furthermore, milling and refining resulted in significant reductions in the concentrations of phenolic acids and methyl-donors in the flour products. In summary, it is well established that bran and germ fractions contain much higher concentrations of major phytochemicals and stronger antioxidant activities than flour fractions, which supports the health benefits of consuming whole grain foods.

Different milling processes and protocols can influence the particle size of whole grain flour and the proportion of bran fraction, thereby affecting the extractability of phytochemicals or their composition. Brewer et al. (2014) evaluated the effect of bran particle size on extractability of bran phytochemicals and antioxidant properties. Their results showed that the amounts of extracted phenolic acids, anthocyanins, and carotenoids as well as the ORAC value increased with decreasing bran particle size. Therefore, it seems that smaller particle sizes are positively related to higher extraction rates of phytochemicals. However, intense milling procedures, especially heat, that lead to smaller particle sizes may also damage the phytochemicals. Also, it must be pointed out that, especially for pilot-scale and industry-scale milling, the recovery rate is usually not 100% and bran loss during processing varies with different milling methods. Milling methods that lead to smaller particles may be accompanied by higher percentages of bran loss. Furthermore, higher extractability of phytochemicals with solvents does not necessarily guarantee higher bioaccessibility in the human digestive tract. Future studies are needed to evaluate the effects of milling and particle size on bioaccessibility of wheat phytochemicals in the digestive tract.

4.3 | Heat pretreatment

Thermal processing generally refers to the procedure whereby whole grains are treated with external heat for a period of time prior to milling. Călinoiu and Vodnar (2020) reported that thermal processing of wheat brans at 80°C for 10 min coupled with ultrasound-assisted extraction enhanced the measured levels of TPC, *trans*-FA, vanillic acid, and *para*-coumaric acid of wheat brans by 22.5%, 39.2%, 95.7%, and 71.9%, respectively. Rico et al. (2020) reported that autoclave treatment increased the amount of extractable free FA from 6.41 to 24.13 mg/100 g bran and increased the content of apigenin-6-C-arabinoside-8-C-hexoside. Ciccoritti et al. (2021) reported that hydrothermal and hot air drying improved AR extractability, changed AR homologue composition, and decreased soluble TPC. On the contrary, Li et al. (2007) reported that thermal processing did not significantly change TPC, ABTS, or ORAC antioxidant activities in purple wheat brans, possibly because the anthocyanins in the purple pericarp were damaged during the processing, while some free phenolics were released. The net effect was that no significant change was observed. In summary, thermal treatments seem to facilitate the release of phytochemicals from cell wall materials and increase their extractability. Heat can also degrade some phytochemicals that are not heat stable such as anthocyanins and some types of vitamins.

4.4 | Enzymatic hydrolysis

Previous studies have reported that enzymatic hydrolysis can release wheat phytochemicals from bound insoluble

fractions and therefore increase their potential bioaccessibility. Wheat phenolic antioxidants mainly exist in insoluble forms bound with cell wall materials. Enzymatic treatments can partially break down the network and therefore release phenolic acids into soluble fractions. Moore et al. (2006) examined the effects of solid-state treatments with Viscozyme L (a cellulolytic enzyme mixture), Pectinex 3XL (a pectinase), Ultraflo L (a blend of β-glucanase and arabinoxylanase), Flavourzyme 500L (a blend of endo- and exopeptidases), Celluclast 1.5L (a cellulase), and porcine liver esterase on the release of phenolic antioxidants from wheat bran. The enzymatic treatments led to the release of phenolic antioxidants such as *trans*-FA from the bound insoluble fractions and consequently increased ABTS/DPPH/ORAC antioxidant activities. Ultraflo L was the most effective and released over 50% of the insoluble *trans*-FA into the soluble fraction. Likewise, Bautista-Expósito et al. (2020) tested 13 commercial glycosidases and found that Ultraflo XL released most of the phenolic acid from the insoluble fraction to soluble fraction. Xue et al. (2020) reported that β-endoxylanase and α-arabinofuranosidase treatments increased the soluble phenolic acid concentrations and antioxidant activities of wheat brans. They further showed that brans prepared by enzymatic treatments had enhanced technological properties for breadmaking. Currently, the concentration of bound insoluble *trans*-FA is almost exclusively determined after NaOH hydrolysis. However, NaOH hydrolysis may not be able to release all the phenolic acids even with an extended hydrolysis time. For studies aimed to quantify total phenolic acids, new protocols combing enzymatic treatments and conventional NaOH hydrolysis might advance our understanding of phenolic acid and cell wall material interactions.

4.5 | Fermentation

The term "fermentation" refers to general fermentation by different microorganism strains, or more specifically to the yeast/sourdough fermentation as a step in breadmaking. Zhai et al. (2015) reported that solid-state fermentation with the Basidiomycete fungus *Agaricus blazei* increased whole grains' TPC, DPPH radical scavenging activity, and superoxide anion radical scavenging ability. Đorđević et al. (2010) investigated the effects of fermentation by lactic acid bacterial species *Lactobacillus rhamnosus* and yeast species *Saccharomyces cerevisiae* on phenolic contents and antioxidant activities of four cereal and pseudo cereal products (buckwheat, wheat germ, barley, and rye). Their results suggested that the microbial activities enhanced their TPC, DPPH activity, and ferric ion-reducing antioxidant power (FRAP). Another study on solid-state fermentation by four fungi (*Aspergillus oryzae* NCIM 1212, *Aspergillus awamori* MTCC No. 548, *Rhizopus oligosporus* NCIM 1215, and *Rhizopus oryzae* RCK2012) reported a 14-fold improvement in soluble TPC (11.61 mg GAE/g grain) in *A. oryzae*-fermented wheat (Bhanja Dey & Kuhad, 2014). This study also reported that soluble extracts of *R. oryzae*-fermented wheat exhibited a maximum of 6.6-fold enhancement of DPPH radical scavenging activities (8.54 μmol TE/g grain) and a 5.0-fold enhancement of ABTS radical scavenging activities (19.5 μmol TE/g grain). Although most fermentation studies reported increases in TPC and antioxidant activities, this was not always the case. For example, Ripari et al. (2019) conducted a fermentation study using 114 bacterial strains and reported that the concentration of some phenolic acids, such as *trans*-FA, decreased during fermentation, possibly due to the metabolism of phenolic acids by the bacteria or the enzymatic activities of decarboxylases, esterases, and reductases. Generally speaking, biotransformation of phenolic compounds in fermented cereal products depends on microbial strains, cereal species, and flour sources (Ferri et al., 2016), and some wheat genotypes are more resistant to fermentation. In addition, wheat phenolics exist in both soluble and insoluble fractions, but some studies on fermentation only considered the soluble fractions. Bacterial and yeast fermentation can release some phenolic compounds from insoluble-bound fractions, and these released phenolics might be metabolized by the microorganisms. Because fermentation may also change the extractability of insoluble phenolics, future studies should characterize both soluble and insoluble fractions.

Changes in wheat product phenolic profiles and antioxidant activities during fermentation in breadmaking have also been described. Tian, Chen, Tilley, et al. (2021) investigated the effect of yeast fermentation on phenolic acid composition and antioxidant in flours from four winter wheat genotypes. The results showed that mixing and fermentation increased the concentrations of soluble phenolic acids, TPC, and ABTS/DPPH/ORAC antioxidant activities, but fermentation did not significantly affect the insoluble-bound phenolics. Antognoni et al. (2019) reported changes in carotenoids, phenolic acids, and antioxidant capacity in wheat bread doughs fermented with different lactic acid bacterial strains and found that some strains caused in situ changes, significantly increasing the concentrations of bioactive compounds in dough during fermentation. This could improve the functional properties of bakery products with higher concentrations of phenolic acids, carotenoids, and other bioactive compounds.

Koistinen et al. (2016) investigated fermentation effects with both baker's yeast and common sourdough starters

including *Candida milleri*, *Lactobacillus brevis*, and *Lactobacillus plantarum* using nontargeted metabolic profiling by liquid chromatography/time-of-flight/mass spectrometry (LC–TOF–MS). Their study identified 118 compounds in sourdoughs with significantly increased concentrations and 69 compounds with significantly decreased concentrations. Compounds with increased concentrations included branched-chain amino acids, metabolites of phenolic acids by microorganisms, and other potentially bioactive compounds; compounds with decreased concentrations included phenolic acid precursors, nucleosides, and nucleobases. Yu and Beta (2015) investigated the effect of fermentation on purple grain wheat; soluble TPC significantly ($p < .05$) increased during mixing and fermentation, from 105.4 to 113.2 mg FA equivalence (FAE)/100 g. Insoluble bound phenolics slightly decreased after 30 min of fermentation but increased significantly ($p < .05$) after 65 min of fermentation. In summary, previous studies generally agreed that fermentation increases the concentration of soluble phenolic acids and antioxidant activity; however, the effects of fermentation on insoluble phenolics were inconsistent among studies. Fermentation conditions (temperature, time, and strains) and wheat genotype may also influence the effects of fermentation.

4.6 | Food processing

It is important to understand the effect of baking and other food-processing steps on wheat products' phytochemical profiles. Lu et al. (2014) reported that baking did not significantly influence the concentration of total *trans*-FA when using refined flour or whole grain flour. Yu and Beta (2015) reported that the process of breadmaking significantly increased soluble phenolic acids and their antioxidant activities but slightly decreased insoluble-bound phenolic acids and corresponding antioxidant activities. Tian, Chen, Tilley, et al. (2021) investigated the effects of baking on four winter wheat genotypes and found that breadmaking significantly increased soluble phenolic acids and antioxidant activities and also slightly increased insoluble-bound phenolic acids and antioxidant activities. Increases of the soluble TPC and antioxidant activity were partially from Maillard reaction products (MRPs), because bread crust exhibited higher TPC and antioxidant activities than bread crumbs. Incorporation of phenolic acids into MRPs was also observed and confirmed by liquid chromatography/time-of-flight/tandem mass spectrometry (LC-QTOF-MS/MS) (Tian, Chen, Tilley, et al., 2021).

The effects of food processing on other products such as puffed kernels, buns, and extrusion items have been reported. Paznocht et al. (2019) found that during bun making, there was degradation of free and esterified carotenoids, which was mainly caused by dough preparation rather than heat treatment. They also reported decreased concentrations of total carotenoids and E- to Z-isomerization of lutein and zeaxanthin during puffing and extrusion (Paznocht et al., 2021). Ramos-Enríquez et al. (2018) reported increased TPC and DPPH values for wheat bran after extrusion. It is possible that the extrusion process degrades phytochemicals (e.g., carotenoids) with relatively lower stability but increases the extractability of other phytochemicals (e.g., phenolic acids).

4.7 | Effect of simulated digestion and colon fermentation

Some in vitro models have been developed to simulate the gastrointestinal digestive effects on the phytochemicals of whole grain food products. These models can be static or dynamic with the latter better mimicking the human digestive tract. However, static models are less expensive and easy to perform (Brodkorb et al., 2019), whereas dynamic models are expensive and therefore not available to most laboratories. Common dynamic models include the TNO Intestinal Model, in vitro Digestion System (IViDiS), and Human Gastric Simulator (HGS) (Thuenemann, 2015). Podio et al. (2019) investigated the effects of in vitro digestion on the phenolic profile and antioxidant activity of whole wheat pasta. They found that gastric digestion significantly increased soluble TPC and the concentration of phenolic acids, but subsequent intestinal digestion did not release further phenolic compounds from the insoluble-bound fraction. Gong, Chi, et al. (2019) evaluated the effect of simulated digestion and fermentation on the potential bioaccessibility of nine different phenolic acids and showed that most phenolic acids in the wheat food matrix had higher bioaccessibility after in vitro digestion (average 57.7%−82.1%) than after in vitro colonic fermentation (21.9%–47.5%). Gong, Gao, et al. (2019) investigated the effects of in vitro digestion on the phytochemical profiles and cellular antioxidant activity of several whole grains including wheat, corn, oat, and rice. Their results indicated that phenolics in whole grains mostly existed in the digested fractions. The proportion of digested phenolics relative to total phenolics ranged from 57.7% in corn to 79.6% in oat. However, most phenolic acids were still in the insoluble-bound form. Therefore, increases in TPC and cellular antioxidant activities might have come from other sources than just phenolics and other phytochemicals. It is possible that simulated digestion releases bioactive peptides that exhibit antioxidant activities (Hu et al., 2020). In

general, there is still very limited literature on the effects of upper gastrointestinal digestion on the potential bioaccessibility of wheat phytochemicals. Hydrolyzed bioactive peptides and saccharides could interfere with the results from colorimetric assays; however, these bioactive peptides might also contribute to the potential health benefits of whole grains and therefore should not be neglected. More studies are needed to systematically investigate these changes and to understand the contribution from both phytochemicals and other types of bioactive compounds generated through protein and carbohydrate hydrolysis and fermentation.

The interplay between phenolic compounds from food sources and gut microbiota has been widely recognized and recently reviewed (Ray & Mukherjee, 2021). Gut microbiota can release phytochemicals from the food matrix and produce new metabolites from phytochemicals. Kroon et al. (1997) reported the release of insoluble-bound FA from DF in the human colon. Hole et al. (2012) examined the effect of probiotic fermentation on whole grain phenolic acids. They showed that fermentation with probiotic strains *Lactobacillus johnsonii* LA1, *Lactobacillus reuteri* SD2112, and *Lactobacillus acidophilus* LA-5 increased the bioaccessibility of whole grain barley phenolic acids (from 2.55 to 69.91 μg/g grain) and that of oat groat (from 4.13 to 109.42 μg/g). Tian, Hu, et al. (2021) similarly found that *Lactobacillus rhamnosus* GG (LGG), a common probiotic strain, can release *trans*-FA from the residues after gastrointestinal digestion. Furthermore, gut microbiota can produce new metabolites from phytochemicals. Braune et al. (2009) found that intestinal microbiota can completely degrade 8-O-4-DFA; FA and 3-(3-hydroxy-4-methoxyphenyl) pyruvic acid were formed in the transition and then converted to homovanillic acid, 3-(3,4-dihydroxyphenyl) propionic acid, and 3,4-dihydroxyphenylacetic acid. A possible degradation pathway for FA and DFA in the gut is depicted in Figure 6.

5 | BIOAVAILABILITY OF WHEAT PHYTOCHEMICALS

Bioavailability can be defined as the fraction of a nutrient or nutraceutical that is available for the human body for physiological function and/or storage (Bohn, 2014). Knowledge on the absorption and metabolism of dietary phytochemicals is important for understanding their potential health benefits. In this section, we review current knowledge on the bioavailability of major wheat phytochemicals. We focus especially on the absorption and metabolism of dietary phenolic acids, ARs, and BXs, which come primarily from whole grain foods.

5.1 | Bioavailability of phenolic acids

As discussed in Section 2, FA is the predominant phenolic acids in whole wheat. FA and other hydroxycinnamic acids such as sinapic acid exist in soluble-free, soluble-conjugated, and insoluble-bound forms. Adam et al. (2002) investigated FA bioavailability in rats using an in situ intestinal perfusion model. Approximately 50% of the ingested free FA from FA-enriched diets was recovered in the urine. This result indicated the high bioavailability of free FA. In contrast, only 3% of the ingested FA from cereal brans was recovered in the urine. The authors concluded that FA bioavailability was determined by the release from food matrix (bioaccessibility) rather than by FA metabolism. By feeding rats with standard diet (containing no FA), pure FA (5.15 mg FA/kg body weight), or bran (4.04 mg FA/kg body weight), Rondini et al. (2004) found that sulfated or sulfoglucuronidated FA was the major (>70%) form of FA in both plasma and urine. The percentages of total FA excretion in urine were 43% and 2.6% for pure FA and wheat bran, respectively. Furthermore, they found increased antioxidative capacity in the plasma after consumption of pure FA-enriched diet and bran-enriched diet.

Mateo Anson et al. (2009) also reported that the bioavailability of FA was determined by its bioaccessibility. In a human intervention study (Kern et al., 2003), six male volunteers consumed 100 g of high-bran breakfast cereal containing 2.45, 16.09, and 240.56 mg of free, soluble-conjugated, and insoluble-bound FA, respectively. The plasma concentration of FA (mainly as FA-glucuronide conjugate) reached a maximum (150−210 nM) between 1 and 3 h and decreased rapidly between 3 and 6 h after meal. The total excretion of FA through urine was 8.10 mg. This amount was substantially higher than the amount of free FA (2.45 mg). This result clearly indicated that some of the ester-linked FA was also bioavailable, possibly due to the feruloyl esterase activity distributed throughout the intestinal tract of humans as previously reported (Andreasen et al., 2001). In terms of the amount of total FA (259.10 mg), the overall FA bioavailability in high-bran breakfast cereal was low (approximately 3%). In summary, free FA has been shown a high bioavailability (approximately 40%−50%). Soluble-conjugated FA is demonstrated as some extent bioavailable, while insoluble FA seems to be very low bioavailable. The overall FA bioavailability from wheat is thus approximately 3%. Processing and pretreatments of wheat brans/flours that release FA from

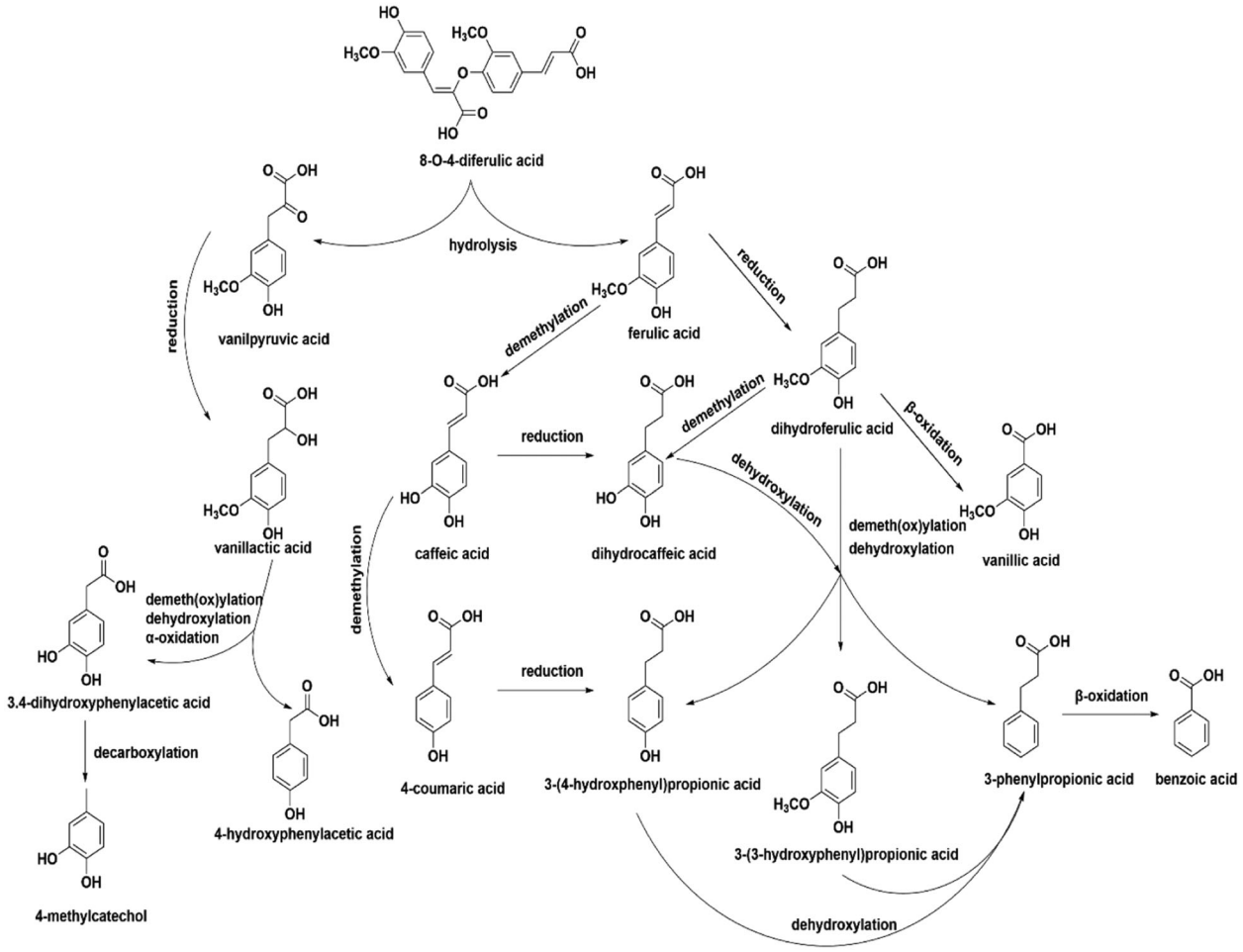


FIGURE 6 Proposed degradation of ferulic acid and diferulic acid by human fecal microbiota in the in vitro colon model. Adapted from Koistinen et al. (2017)

insoluble forms to soluble forms may likely increase its bioavailability.

5.2 | Bioavailability of ARs

Whole grain wheat, rye, and barley are the only food sources of ARs, making ARs and their metabolites potential biomarker for whole grain intake. 3-(3,5-Dihydroxyphenyl)-1-propanoic acid (DHPPA) and 3,5-dihydroxybenzoic acid (DHBA) have been identified as the major AR metabolites in both plasma and urine (Söderholm et al., 2011). However, to our knowledge, the absorption pathway of ARs has not been fully characterized. Landberg et al. (2014) suggested that ARs be absorbed mainly via passive diffusion and to some extent via transportation by scavenger receptor class B (SR-BI). In a human study, 10 volunteers consumed rye-bran-enriched diets. Approximately 60% of ARs were taken up or converted in the small intestine (Ross et al., 2003). This observation suggested that ARs might have a high bioavailability. Landberg et al. (2006) evaluated plasma kinetics and the relative bioavailability of ARs in humans after a single intake of 120 g rye bran that contains 190 mg ARs. The plasma AR concentration reached the maximum concentration at 3.4 μM after 6.5 h. The study also found that the bioavailability of different AR homologs increased with the length of the side chain. The bioavailability of AR25 was five times higher than that of AR17. In another human study including 166 participants for 18 or 24 weeks, Magnusdottir et al. (2013) found that plasma AR concentration was significantly higher ($p < .001$) in the whole grain group than that in the control group. This result confirmed the bioavailable ARs and further indicated their potential as a biomarker for whole grain intake. In summary, ARs in whole grain wheat and rye are of high bioavailable. Further studies are necessary to fully investigate their biological functions.

5.3 | Bioavailability of BXs

Similar to ARs, dietary BXs are primarily found in wheat and rye grains. To our knowledge, there was a limited

number of studies regarding the bioavailability of BXs, and the absorption mechanism of BXs has not been fully understood. Adhikari et al. (2012) evaluated the absorption and metabolism of BXs in rats. The rats were fed a rye-enriched diet containing 4.8 μmol of total BXs. The total level of BXs recovered in the urine was 1.2 μmol, which was approximately 25% of the total dietary intake. DIBOA-glc and HBOA-glc were found to be the major metabolites in the plasma and urine. In a human study by Beckmann et al., 2013, volunteers consumed 48 g of whole rye foods daily for the first 4 weeks and then 96 g of whole rye foods daily for another 4 weeks. The study found that HBOA-glc was the major metabolite from rye bread consumption. Another human study with 20 volunteers evaluated the absorption, metabolism, and excretion of dietary BXs after a daily intake of 143 μmol of total BXs from rye (Adhikari et al., 2013). The authors confirmed that HBOA-glc was the major BXs in both plasma and urine. The plasma BX concentration reached its maximum at 3 h after consumption. In addition, the study identified sulfate and glucuronide conjugates of HBOA and BIOBA, indicating substantial phase II detoxification metabolism of BXs after absorption. In summary, current studies indicated that BXs are bioavailable in humans, although the absorption rate (percentage of the total amount in food) has not been reported yet.

5.4 | Bioavailability of flavonoids

The bioavailability of flavonoids has been extensively characterized and reviewed (Ross & Kasum, 2002; Thilakarathna & Rupasinghe, 2013; Ziberna et al., 2014). Generally speaking, flavonoids have a low bioavailability, which may be variable due to different chemical structures of the flavonoids and food matrices (Yang et al., 2018). Passive diffusion in the intestine was found to be the main absorption pathway (Kay, 2006), but active uptake of quercetin 3-O-glucoside via sodium-glucose transport proteins and absorption through lactase phlorizin hydrolase were also reported (Dai et al., 2015; Wolffram et al., 2002). Since common bread wheat is not generally considered a significant source of dietary flavonoids, there has not been a study on flavonoids' bioavailability in common wheat products. Colored grain, by contrast, may be a good source of anthocyanins. Talavéra et al. (2006) reported that, in rats, the urinary excretion of bilberry anthocyanins and their metabolites was 0.22% of the ingested dose, suggesting low bioavailability of the anthocyanins. However, gut microbiota may degrade flavonoids into flavonoid metabolites that may be easily absorbed (Oteiza et al., 2018).

5.5 | Bioavailability of carotenoids

Since humans cannot synthesize carotenoids and have to rely on dietary sources, the bioavailability of carotenoids from food sources has been a topic of interest for a long time (Fernández-García et al., 2012). Traditionally, it was believed that carotenoid absorption occurs through passive diffusion (Parker, 1996). Recent studies, however, identified that several lipid transporters, namely, scavenger receptor class B type 1 (SRB1), a cluster of determinant 36 (CD36), and Niemann–Pick C1-like 1 protein (NPC1L1), also play a role in the intestinal absorption of carotenoids (Reboul, 2013). The bioavailability of carotenoids depends on the chemical structure, content of fat in the diet, and food matrix. It was estimated that consumption of 3–5 g of fat per meal was necessary for the absorption of carotenoids (van het Hof et al., 2000). Lutein is the major type of carotenoids in wheat. To our knowledge, no study has evaluated lutein's bioavailability in wheat-based foods. A human study indicated that the bioavailability of lutein from vegetables was five times higher than that of β-carotene (van het Hof et al., 1999). This was possibly due to the higher solubility of lutein in fat. Lienau et al. (2003) reported that 12.8%–26.2% of lutein in vegetables can be absorbed by humans. Lutein and zeaxanthin in egg yolk were also found to be of high bioavailable (Handelman et al., 1999). Since lutein mostly exists in free, nonesterified forms in wheat, it is expected that wheat lutein may be also of considerable bioavailable.

5.6 | Bioavailability of phytosterols

After phytosterols are incorporated into micelles, they are absorbed into the enterocytes via the sterol transporter NPC1L1 (Le Goff et al., 2019). However, the bioavailability of phytosterols has been found to be limited. In a recent review paper, Feng et al. (2021) stated that less than 5% of phytosterols could be absorbed by healthy humans. In wheat, sitosterol is the predominant phytosterol and accounts for over 50% of the total sterols (Nurmi et al., 2008). To our knowledge, the bioavailability of sitosterol from wheat has not been evaluated. Duchateau et al. (2012) reported that the oral absolute bioavailability of sitosterol from pulse was just 0.41%. However, it should be noted that a low bioavailability does not preclude the health benefits of phytosterols as described in Section 6.

5.7 | Bioavailability of tocopherols and tocotrienols (vitamin E)

As with carotenoids, passive diffusion was believed to be the major absorption mechanism for vitamin E, although recent studies reported that Niemann–Pick C1-like 1 protein (NPC1L1), scavenger receptor class B type 1 (SRB1), and CD36 also played a mediating role (Szewczyk et al., 2021). The bioavailability of tocopherols and tocotrienols depends on the chemical structure and food matrix. For example, Drotleff et al. (2014) reported that tocotrienols from barley oil (rich in α-tocotrienol) had a significantly higher bioavailability than tocotrienols from palm oil (rich in γ-tocotrienol). Since vitamin E is not soluble in water but soluble in fat, it is believed that fat content in the diet can significantly influence vitamin E's bioavailability. In a human study, five participants consumed vitamin E-fortified apples together with different amounts of fat (Bruno et al., 2006). The results showed that approximately 10% of α-tocopherol was absorbed in the absence of fat, while 33% of α-tocopherol was absorbed with the breakfast containing 11 g fat. Studies on vitamin E's bioavailability from wheat are limited. Kahlon et al. (1986) reported that in rats, wheat bran vitamin E was not bioavailable. By contrast, Mitchell et al. (1996) reported that the bioavailability of vitamin E in whole grain cereal and cornflakes was generally high and comparable to that of the tocopherol acetate standard in rats. More studies seem warranted to determine the bioavailability of vitamin E in wheat.

6 | HEALTH BENEFITS OF WHEAT PHYTOCHEMICALS

The benefits of DF in whole grain products have been well documented and widely accepted (Anderson et al., 2009). The benefits of phytochemicals from other food sources, especially fruits, vegetables, and teas, have also been well characterized (Li et al., 2021; Wu et al., 2021). In vivo evidence supporting the benefits of whole grain phytochemicals has not been well summarized, although they are believed to have similar health impact as other sources. Given the current research gap, in this section, we try to focus on animal/human studies that indicate the potential health benefits of wheat phytochemicals and document possible mechanisms (Table 5). The benefits of natural vitamin E from various sources are well established and therefore are not included in this section.

6.1 | Obesity and diabetes management

Type II diabetes is often associated with obesity and is characterized by elevated blood glucose, attenuated insulin sensitivity, and high cholesterol (Colosia et al., 2013). A balanced diet was a basic tool to control blood glucose levels (Gil et al., 2011). An increased intake of whole grain foods had been associated with a reduced risk of type II diabetes (Monro & Shaw, 2008; Montonen et al., 2003). The antidiabetic effects of phenolic acids from all sources have been widely recognized and reviewed (Vinayagam et al., 2016). Biskup et al. (2017) pointed out that phytochemicals, such as phytic acid, phenolic acids, and ARs, contribute to the control of blood glucose levels, insulin sensitivity, and hyperinsulinemia. FA, the most abundant phytochemical in whole grain, exhibited antidiabetic effects through several mechanisms. Adisakwattana et al. (2009) found that FA slowed down sugar digestion and hence the rise of blood glucose after a meal. Son et al. (2011) evaluated the effect of FA on the metabolism of C57BL/6 mice fed with a high-fat diet. The results showed that 0.5% of FA in the diet significantly decreased blood glucose levels and activities of glucose-6-phosphatase (G6pase) and phosphoenolpyruvate carboxykinase (PEPCK). FA also led to higher insulin concentrations and glucokinase (GK) activity compared with the control group. This insulin-releasing effect of FA had been reported previously (Adisakwattana et al., 2008). Ramar et al. (2012) investigated the protective effect of FA (10 mg/kg body weight) against alloxan-induced diabetes in mice. The results showed that FA decreased lipid peroxidation and the level of nuclear transcription factor (NF-κB), a known proinflammatory factor. Similar protective effects were reported by another study (Yin et al., 2014). Narasimhan et al. (2015) fed diabetic rats by 50 mg/kg body weight of FA and found a reduced GLUT2 expression that was usually overexpressed in diabetic conditions by impairing the interaction between transcription factors (SREBP1c, HNF1α, and HNF3β) and the GLUT2 gene promoter. Huang et al. (2018) showed that oral administration of 600 mg/kg body weight/day of feruloylated oligosaccharides (Fos), the main form of esterified FA-bound oligosaccharides, significantly lowered the levels of fasting plasma glucose (FPG), fasting insulin, aspartate transaminase, creatine kinase, and lactate dehydrogenase in rat plasma, which might help with the management of type II diabetes.

ARs, another major phytochemical in wheat, also exhibited direct or indirect protective effects against diabetes. In vitro studies reported that ARs, especially AR21, significantly inhibited the activity of glycerol-3-phosphate

TABLE 5 Health benefits of wheat phytochemicals supported by in vivo experiments

Health benefits	Phytochemicals	Experiment model	Possible mechanisms	References
Weight control	Ferulic acid and anthocyanins	Mice	Prevented high-fat-induced obesity in mice by modulating SIRT1, AMPK, and IL-6-associated metabolic and inflammatory pathways	Luna-Vital et al., 2020
Diabetes management	Ferulic acid	C57BL/6 mice fed with high-fat diet	Decreased blood glucose level and glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities. Increased inulin level and glucokinase activity.	Son et al., 2011
Diabetes management	Ferulic acid	Mice with diabetes	Deceased lipid peroxidation and level of nuclear transcription factor (NF-κB), a known proinflammatory factor	Ramar et al., 2012; Yin et al., 2014
Diabetes management	Ferulic acid	Rats with diabetes	Reduced glucose transporter protein (GLUT2) expression by impairing the interaction between transcription factors (SREBP1c, HNF1α, and HNF3β) and GLUT2 gene promoter	Narasimhan et al., 2015
Diabetes management	Feruloylated oligosaccharides (main form of ferulic acid bound oligosaccharides by esterification)	Rats	Decreased levels of fasting plasma glucose (FPG), fasting insulin, aspartate transaminase, creatine kinase, and lactate dehydrogenase in rat plasma	Huang et al., 2018
Diabetes management	Phytic acid and alkylresorcinols	Human	Control of blood glucose levels, insulin sensitivity, and hyperinsulinemia	Biskup et al., 2017
Reduced risk of cardiovascular diseases	Ferulic acid	Hypertensive rats	Improved the structure and function of the heart, blood vessels, liver, and kidney	Alam et al., 2013
Reduced risk of cardiovascular diseases	Ferulic acid	Human (randomized, double-blind, placebo-controlled trial with 48 subjects)	Decreased total cholesterol (8.1%; $p = .001$), LDL-C (9.3%; $p < .001$), triglyceride (12.1%; $p = .049$), and oxidized LDL-C (7.1%; $p = .002$).	Bumrungpert et al., 2018
			Decreased the oxidative stress biomarker MDA (24.5%; $p < .001$) and inflammatory biomarkers hs-CRP (32.66%; $p < .001$) and TNF-α (13.06%; $p < .001$)	

(Continues)

TABLE 5 (Continued)

Health benefits	Phytochemicals	Experiment model	Possible mechanisms	References
Reduced risk of cardiovascular diseases	Phenolic acids and flavonoids	Rats	Attenuated doxorubicin induced cardiotoxicity	Sahu et al., 2019
Reduced risk of cardiovascular diseases	Alkylresorcinols	Mice	Increased fecal cholesterol excretion by 39.6%; reduced blood cholesterol concentration by 30.4%; enhanced expression of hepatic cholesterol synthetic genes	Oishi et al., 2015
Reduced risk of cardiovascular diseases	Alkylresorcinols	Mice	Inhibited LDL oxidation; increased fecal cholesterol excretion	Horikawa et al., 2017
Reduced risk of cardiovascular diseases	Phytosterols from corn oil	Human	Reduced cholesterol absorption	Ostlund et al., 2002
Reduced risk of cardiovascular diseases	Phytosterols from wheat germ	Human	Reduced cholesterol absorption	Ostlund et al., 2003
Reduced risk of cardiovascular diseases	Phytosterols	Human with a total cholesterol of >5.5 mmol/L	Decreased level of low-density lipoprotein	Clifton & Keogh, 2018
Reduced risk of cardiovascular diseases	Total antioxidant capacity (TAC) determined by ORAC assay	Human (31,035 CVD-free women and 5680 women with CVD aged 49–83 years)	Dietary TAC is inversely associated with total stroke among CVD-free women and hemorrhagic stroke among women with a CVD history	Susanne et al., 2012
Reduced risk of colorectal cancer	Alkylresorcinols	Mice	Synergistic effect with fiber microbial metabolite butyrate	Zhao et al., 2019
Reduced risk of colorectal cancer	Ferulic acid	Mice with colon cancer	Upregulated P53 expression; inhibited cell proliferation and promoted apoptosis	Alazzouni et al., 2021
Neuroprotective effects	Phytosterols	Aged rats with high-cholesterol-induced cognitive deficits	Alleviated neuroinflammation; inhibited degeneration	Rui et al., 2017

dehydrogenase and reduced triglyceride accumulation in 3T3-L1 cells (Luyen et al., 2015; Rejman & Kozubek, 2004). Another in vitro study found that ARs from rye inhibited activities of adipocyte lipolysis and hormone-sensitive lipase, which could reduce the level of free fatty acid and consequently the risk for hypertension and diabetes (Samuel et al., 2010). Oishi et al. (2015) found that wheat ARs increased glucose tolerance and insulin sensitivity in mice by suppressing hepatic lipid accumulation and intestinal cholesterol absorption, which subsequently suppressed diet-induced obesity. Anti-inflammatory activity of phytochemicals may also help reduce the risk and mortality of diabetes. Roager et al. (2019) found a negative correlation between serum interleukin 6 (IL-6), a common indicator of inflammation, and plasma concentrations of total ARs.

6.2 | Reduced risk of CVDs

CVDs include stroke, coronary heart disease (CHD), hypertensive diseases, and blood vessel diseases (Sanchis-Gomar et al., 2016). An elevated level of low-density lipoprotein cholesterol (LDL-C) is considered the major risk factor for CVDs (Wilson et al., 1998). Besides DFs, various wheat phytochemicals have exhibited protective effects against CVDs. Several studies showed that individuals consuming three or more portions of whole grain cereal food per day have a 20%–30% lower risk of CVDs than those consuming low quantities of whole grain (Gil et al., 2011). Yamagata and Yamori (2020) suggested that the flavonoid compounds from fruit, vegetables, and whole grains help reduce the risk of CVDs caused by endothelial dysfunction-related atherosclerosis. Sahu et al. (2019) reported that polyphenolic extracts from whole grain wheat attenuated doxorubicin-induced cardiotoxicity. The study further indicated that polyphenolic extracts exhibited better cardioprotective capacity than pure FA and apigenin. Alam et al. (2013) found that FA supplementation (50 mg/kg/day) improved the structure and function of the heart, blood vessels, and kidney in hypertensive rats. A randomized, double-blind, placebo-controlled trial of 48 human subjects confirmed the benefit of FA (Bumrungpert et al., 2018). In the study, FA supplementation (1000 mg daily for 6 weeks) significantly decreased total cholesterol (8.1%; $p = .001$), LDL-C (9.3%; $p < .001$), triglyceride (12.1%; $p = .049$), and oxidized LDL-C (7.1%; $p = .002$) compared with the control group. FA supplementation also significantly decreased the oxidative stress biomarker MDA (24.5%; $p < .001$) and inflammatory biomarkers hs-CRP (32.66%; $p < .001$) and TNF-α (13.06%; $p < .001$).

In a mouse model, Oishi et al. (2015) found that diet enriched with 0.4% ARs from wheat bran increased fecal cholesterol excretion by 39.6% and reduced blood cholesterol levels by 30.4%. Similarly, Horikawa et al. (2017) reported that wheat ARs reduced plasma cholesterol concentrations by 32% in mice without affecting hepatic and fecal bile acid concentrations. In particular, phytosterols can inhibit the absorption of cholesterol in the small intestine. An excellent review on phytosterols from all sources and their prevention of CVDs has been previously published (Gylling et al., 2014). Phytosterols from cereal grains also exhibited cholesterol-lowering effects. Ostlund et al. (2002) developed a technique that removed natural phytosterols from normal corn oil. In a subsequent human study of 25 volunteers for 2 weeks, they found that cholesterol absorption was 38.0% $\pm$ 10.2% higher for participants consuming sterol-free corn oil compared to those consuming normal corn oil ($p = .005$; $n = 10$). Adding 150 and 300 mg of phytosterols back to the sterol-free corn oil reduced cholesterol absorption by 12.1% $\pm$ 3.7% ($p = .03$; $n = 5$) and 27.9% $\pm$ 9.1% ($p = .01$; $n = 10$), respectively. A similar human study showed that plasma cholesterol was 42.8% higher after consumption of phytosterol-free wheat germ compared with original wheat germ (Ostlund et al., 2003).

6.3 | Reduced risk of colorectal cancer

The potential role of phytosterol in reducing cancer risks has been recognized for a long time (Shahzad et al., 2017). For example, Raicht et al. (1980) reported the protective effect of phytosterol on rats fed with methyl nitrosourea, a well-known chemical carcinogen. The result showed that adding 0.2% β-sitosterol in the diet for 28 weeks reduced the odd of colon tumor from 54% to 33% and the severity of tumor condition from 2.4 tumors/tumor-bearing animal to 1.3 tumors/tumor-bearing animal. A meta-analysis suggested that there be an inverse association between whole-grain intake and colorectal cancer (Benisi-Kohansal et al., 2016). DF and phytochemicals in the bran fraction were postulated to contribute to this effect. DF might contribute to higher stool mass and the production of beneficial short-chain fatty acids (SCFAs). Individuals with colorectal cancer had lower abundances of *Lactobacillus* spp. And other SCFA-producing bacteria, such as *Clostridium* and *Roseburia* spp., and the prebiotic effects of wheat phytochemicals may also contribute to colon health (Costabile et al., 2008; Gong, Chi, et al., 2019).

Wheat bran demonstrated a consistent protective effect against colon cancer, while corn and oat brans did not (Sang et al., 2006). Therefore, wheat brans may contain unique components that have strong anticancer effects. ARs, a unique group of phytochemicals in wheat and rye, may be an important contributor to colon health. The

cytotoxic activity of ARs on various cancer cell lines has been extensively recognized (Kruk et al., 2017). Using human colon cancer cell (HCT-116 and HT-29) models, Zhu et al. (2011) identified ARs as the main bioactive components in wheat bran that inhibited the growth of colon cancer cells. Furthermore, Zhao et al. (2019) reported that ARs in wheat bran might provide health benefits through synergistic effects with fiber microbiota metabolites. The observed synergistic effect was associated with the induction of cell apoptosis, autophagy, and endoplasmic reticulum (ER) stress pathways. More importantly, the authors claimed that the required AR concentration was achievable through daily whole wheat consumption.

Another unique contribution of whole grain consumption to colon health can be attributed to the insoluble-bound phenolic acids (Liu, 2007). The insoluble-bound phenolic acids can survive upper gastrointestinal digestion and reach the colon. The gut microbiota may release FA so they can exhibit their antioxidative, anti-inflammatory, and anticancer potential in the colon. Alazzouni et al. (2021) compared the anticancer activity of FA (50 mg/kg body weight, three times a week for 4 weeks) and an anticancer drug 5-flurouracil in rats with colon cancer. FA significantly ($p < .01$) upregulated p53 expression by approximately fivefold. The results suggested a therapeutic effect of FA against colon cancer by inhibiting proliferation and inducing apoptosis. Zheng et al. (2019) also found that poly-FA could inhibit colon tumor growth in mice. The study further showed that poly-FA could serve as a drug nanocarrier for colon cancer therapy.

7 | CONCLUSIONS AND PERSPECTIVES

In this review, we provided a comprehensive and critical account on the fundamental knowledge and recent progress of wheat phytochemical research. More studies are needed to understand the chemistry of in situ cross-linkages between phytochemicals and cell wall materials, esters and/or glycosides of carotenoids, vitamin E, and phytosterols. This review critically assesses in vitro assays for the quantification of total phenolics, total flavonoids, and antioxidant capacities. Results from these assays need to be interpreted with caution. Future in vivo studies are advised to focus on specific compounds and limit the use of nonspecific "total" in vitro assays. Processing effects also need to be interpreted carefully since processing could physically change the extractability of some phytochemicals or chemically modify them. Animal/human experiments supporting the health benefits of wheat phytochemicals are summarized in this review. Previous studies tend to focus on individual or very few phytochemicals, but several components are likely to be synergistic in function. Future studies are warranted to investigate the cumulative effect of diverse phytochemicals.

In summary, significant progress has been made in understanding the chemistry, occurrence, and processing effects of wheat phytochemicals. However, inconsistencies in interpretation are possible due to the lack of standard sampling protocols and analytical methods. Greater knowledge of the effect of genotypes, growing environments, and management practice will be important for developing and producing functional wheat products with enhanced and repeatable phytochemical profiles. Results of current studies are mostly from small groups of wheat genotypes. Collaborations are needed to perform more sophisticated experimental studies involving a wider range of wheat genotypes grown across more environments and years. It will be necessary to include wheat breeders and producers, cereal chemists, food engineers, nutritionists, clinical scientists, data analysts, and food manufacturers in these collaborations in order to achieve a widespread consumer awareness of the health benefits of whole grain products. The ultimate goal is to increase the acceptability and consumption of whole grain products.

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AUTHOR CONTRIBUTIONS

W.T. and Y.L. conceptualized the idea of the study, performed formal analysis, and designed the methodology. W.T. curated the data, performed validation and visualization, and wrote the original draft. W.T., Z.H., and Y.L. performed investigation. All the authors reviewed and edited the manuscript. Y.Z., W.W., D.W., M.T., G.Z., Z.H., and Y.L. provided resources. Z.H. and Y.L. acquired funding, administered the project, and performed supervision.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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