Epidemiological studies have demonstrated that regular consumption of whole grains is associated with reduced risk of many diseases, including cardiovascular disease, certain cancers, and type 2 diabetes (3–5). Although it is widely accepted that fruits and vegetables provide significant amounts of natural antioxidants, much less emphasis has been put on the antioxidants found in grains. Grains contain a variety of unique phytochemicals with antioxidant activities, and the phenolics found in grains, in particular, could complement the antioxidants found in fruits and vegetables (2,36).

Avenanthramides are found exclusively in oats (14,15); alk(en)ylresorcinols are found in large quantities in rye and wheat (31); and ferulic acid accounts for almost all of the phenolic acid content in the wheat grain (32,54).

Although the avenanthramides, alk(en)ylresorcinols, and ferulic acid content in grains is high, their bioavailability is generally poor, typically ranging from 2 to 20% (22). Because the body treats them as xenobiotics, or foreign substances, they must overcome many barriers, such as solubility, permeability, metabolism, and excretion, to become bioavailable (22,52). This article provides an overview of the major phenolic antioxidants found in grains (ferulic acid, alk(en)ylresorcinols, and avenanthramides), focusing on their metabolism and bioavailability.

### Health Benefits of Consuming Foods Rich in Antioxidants

Reactive oxygen species (ROS) are a diverse group of reactive, short-lived, oxygen-containing species, such as superoxide (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), and hydroxyl radicals (•OH). When produced in excess, they result in oxidative stress and can damage proteins, lipids, and DNA (21). Oxidative damage increases the risk of chronic diseases, such as cancer, metabolic disorders, and cardiovascular disease (55). Antioxidants are compounds that interact with ROS and prevent cellular damage by terminating the otherwise harmful chain reactions these unstable molecules set in motion. Therefore, increased consumption of fruits, vegetables, and whole grains, which contain high levels of antioxidants, is recommended.

### Antioxidants in Grains

Miller et al. (45) have demonstrated that the average antioxidant activity of cereal products equals or exceeds that of most fruits and vegetables (Fig. 1). They point out that although common fruits (with an antioxidant content of 1,200 Trolox equivalents [TE]/100 g) and vegetables (450 TE/100 g) are generally recognized as good sources of antioxidants, whole grain breakfast cereals (2,600–3,500 TE/100 g) actually contain significantly higher amounts of antioxidants on a per weight basis. The phytochemicals that contribute to the high antioxidant capacity of grains include phenolics, carotenoids, and vitamin E (7,37). Phenolics are the most abundant and well studied (Fig. 2).

### Phenolics in Grains

Phenolics are a group of phytochemicals found in plants that have at least one aromatic ring bearing one or more hydroxyl groups. These molecules are generally classified as phenolic acids, flavonoids, stilbenes, and lignans based on their structure and function (35). In plants, phenolics contribute to color, are important for reproduction and growth, and help protect against damage from UV light, pathogens, parasites, and predators. In humans, phenolics may help reduce the risk of developing certain chronic diseases, which is why they have been studied so extensively (37). The most common phenolics found in grains are phenolic acids (primarily in the form of ferulic acid) and alk(en)ylresorcinols and avenanthramides, which are unique...
to grains. The chemical structures of these molecules are displayed in Figure 3, and the phenolic contents of rye, wheat, rice, corn, and oat flours are presented in Table I (9,43).

Ferulic acid is the most abundant phenolic acid found in cereal grains; in wheat, it represents up to 90% of the total polyphenol content (32,54). The aleurone and pericarp layers, which constitute the outer parts of the wheat grain, contain 98% of the total ferulic acid (38). Not surprisingly, the aleurone fraction of wheat has the highest antioxidant capacity, with ferulic acid contributing 60% of the antioxidant effect (41). Grain phenolics usually exist in free, soluble conjugate, and insoluble bound forms, and form has a huge effect on bioavailability. Phenolics in free and soluble forms often have much higher bioavailability compared with those in bound form. The quantities of free, soluble, bound, and total ferulic acid found in wheat, rice, corn, and oat are summarized in Table II (2).

Alk(en)ylresorcinols are a group of phenolic lipids found in large quantities in the bran of wheat and rye (49); they are not found in oats (29). Alk(en)ylresorcinols consist of a phenolic ring with two hydroxyl groups and a long (typically C15–C25) nonisoprenoid side chain attached at the C5 position. This side chain can be saturated or monosaturated or can contain two double bonds between carbon atoms (6,31). They are of interest due to their potential health benefits (6,31). Although their antioxidant potential has been demonstrated in vitro (19,20,28,46), more studies are needed to determine whether this effect is also seen in vivo.

Avenanthramides are a group of hydroxycinnamoylanthranilate alkaloids that occur at their highest concentration in the bran and outer layers of oat kernels (47). More than 35 forms have been identified (23), of which avenanthramides 2p, 2f, and 2c are the most abundant (14). Their potent antioxidant activity has been demonstrated both in vitro and in vivo (9,11,12,17,33,47). We have conducted in vitro research (unpublished) that shows avenanthramides have greater antioxidant activity than either ferulic acid (24) or alk(en)ylresorcinols (19), as measured by the oxygen radical absorbance capacity (ORAC) assay: 37,555, 23,038, and 18,884 μM TE/g for avenanthramide 2c, 2p, and 2f, respectively; 13,000 μM TE/g for ferulic acid; and <200 μM TE/g for alk(en)ylresorcinols. In addition, Chen et al. (11) have demonstrated that avenanthramides have antioxidant activity in humans. Specifically, they found that after participants consumed 1 g of an avenanthramide-enriched mixture extracted from oats, levels of the reduced form of glutathione in their plasma were elevated.

**Fig. 1.** Average antioxidant activity of different foods. Data were drawn from analysis of 3 melons, 20 vegetables, 12 fruits, 2 white breads, 1 rice cereal, 3 corn cereals, 2 whole grain breads, 3 whole grain oat cereals, 3 whole wheat cereals, 2 whole grains with raisins, and 5 berries. TE = Trolox equivalents. (Reproduced with permission from the publisher, Taylor & Francis [45])

**Fig. 2.** Chemical structures of select antioxidants found in grains: phenolics, vitamin E, and carotenoids.
Metabolism of Phenolics

In foods, most phenolics are present as esters, glycosides, or polymers that are esterified or bound to polysaccharides in the cell wall. Once consumed, the various phenolic compounds are believed to be metabolized via common pathways (51). To exert beneficial health effects, they must either be absorbed into the blood and transported to target tissues or organs or reach the colon, where they can interact with the microflora. Thus, the manner in which they are metabolized determines their bioactivity.

After consumption, the first step that determines the proportion of phenolics available for absorption involves bioaccessibility. Bioaccessibility refers to the portion of a compound that is released from the food matrix in the gastrointestinal lumen, making it available for intestinal absorption (50). Mateo Anson et al. (42) examined the bioaccessibility of ferulic acid from different wheat fractions and breads using an in vitro system that simulates GI transit and digestion. They determined that <1% of ferulic acid bound to indigestible polysaccharides was bioaccessible; however, when free ferulic acid was added to flour, bioaccessibility increased to roughly 60%. This indicates the form in which phenolics are present in the food matrix plays an important role in how bioaccessible, and therefore how bioavailable, they are.

Phenolics released from their food matrices must be absorbed in the intestinal lumen, although the mechanisms by which this occurs are not completely understood (10,38,52,56). The amount of phenolic compound available for absorption depends largely on its molecular structure (53). Hydrophilic phenolics, such as glycosides, are too polar and sometimes too large to penetrate enterocytes, the absorptive cells lining the intestine. Instead, they must be hydrolyzed by β-glucosidases or lactase-phlorizin hydrolase to release their sugar moieties, which makes them easier to absorb. However, the aglycone compound produced by hydrolysis has low solubility, which can slow absorption. A good balance between solubility (hydrophilicity) and permeability (lipophilicity) is important for entry of a phenolic into enterocytes (18,22). Transport mechanisms into the enterocyte include passive diffusion, facilitated diffusion, and active transport. However, how an individual phenolic compound enters into enterocytes is largely unknown. Based on their structure, most phenolics do not have the necessary physiochemical properties for passive transport and, therefore, may require transmembrane transporters. For example, in rats, cinnamic and ferulic acids are actively transported from the jejenum to the enterocyte by the Na+-dependent transporter (1).

Once inside the enterocyte, phenolics are subjected to phase 1 and 2 enzymes. Phase 1 and 2 metabolism yields more hydrophilic compounds, facilitating their elimination via bile and urine (52), which may decrease their bioavailability by reducing length of exposure. The reactions catalyzed by phase 1 enzymes include oxidation, reduction, and hydrolysis. Oxidation is the most predominant of these reactions and is performed primarily by cytochrome P450-dependent mixed-function oxidases (CYPs). Phase 1 enzymes facilitate phase 2 conjugation reactions by exposing or adding a functional group, such as a hydroxyl group, to the molecule. Phase 2 enzymes include uridine diphosphoglucuronosyl transferases, sulfotransferases, and glutathione-S-transferases. These three enzymes catalyze the conjugation of phenolics with glucuronic acid, a sulfo moiety, or glutathione. Conjugation is quite efficient, and most polyphenols are conjugated after leaving the enterocyte. Some phenolic aglycones or their metabolites may be effluxed from the enterocyte back into the intestinal lumen by ATP-binding cassette (ABC) transporters, P-glycoprotein (Pgp/ABCB1/MDR1), multidrug resistance-associated protein 2 (MRP2/ABCC2), and/or breast cancer resistance protein (BCRP/ABCG2) (23). The efflux process, as well as the metabolic processes that increase hydrophilicity, and hence elimination, represent defense mechanisms that protect the human body from exposure to xenobiotics. However, they may also contribute to the poor bioavailability of phenolics.

Next, phenolic aglycones and their metabolites are carried into hepatocytes via the portal vein, where phase 1 and 2 metabolism continues (56). From the liver, metabolites can either enter the main circulatory system or be excreted with bile into the small intestine (10). In the latter case, they can either be eliminated with feces or enter the enterohepatic cycle and be reabsorbed after deconjugation by the intestinal microflora. Enterohepatic recycling may result in greater length of exposure to phenolics and their metabolites (10,52), thereby increasing the potential for these compounds to provide beneficial effects. In the former case, they enter the

Fig. 3. Chemical structures of three phenolics found in grains.
circular system, phenolics and their metabolites are bound to plasma proteins, primarily albumin, and they are transported to target tissues and organs or eliminated via urine. The phenolics and their metabolites are typically excreted in urine as small conjugates, such as monosulfates, in amounts that are roughly correlated with their maximum concentration in plasma (38).

A large proportion of phenolics is not absorbed in the small intestine and instead travels to the colon. There, phenolics encounter colonic microflora, which hydrolyze and metabolize them into many small metabolites. These small metabolites are then absorbed. Identifying and quantitating microbial metabolites is of great importance for determining the metabolic fate and biological functions of phenolics. It may be difficult to predict the metabolites produced with precision due to the diversity in colonic microflora among individuals. However, some active metabolites produced by microflora have been identified and could be used as biomarkers of phenolic compound intake (38). Although the composition of the colonic microflora plays a major role in the metabolism of phenolics, the metabolites themselves influence the composition of the microflora (10,38). Thus, phenolics are considered potential prebiotics.

Ferulic acid, which is commonly found esterified to arabinoxylosyl and as feruloylquinic acid in cereal grains (13), is an example of a phenolic compound that is largely metabolized in the colon. Metabolism occurs in the colon due to the presence of colonic esterases that cleave ferulic acid to its free form; the small intestine does not possess these enzymes. Thus, the low bioaccessibility of ferulic acid in its natural form in wheat fractions and bread is due to the inability of bound ferulic acid to be released and absorbed in the small intestine.

Because alk(en)ylresorcinols are phenolic lipids, they do not follow the same metabolic pathways as most other phenolic compounds. Instead, they typically follow the pattern of tocopherol metabolism (31). Alk(en)ylresorcinols may be absorbed into enterocytes either via passive diffusion or active transport by scavenger receptor class B molecules. Once inside the enterocytes, they are most likely assembled into chylomicrons, entering circulation through the lymphatic system, or packaged into high-density lipoprotein (HDL) particles. In the blood, alk(en)ylresorcinols are transported in association with lipoproteins, mainly very low-density lipoprotein (VLDL) and HDL, and erythrocyte membranes (34). Alk(en)ylresorcinols that do not accumulate in tissues are taken up by the liver, where they are either reassembled into lipoproteins and secreted back into circulation or metabolized into 3,4-dihydroxybenzoic acid and 3-(3,5-dihydroxyphenyl)-1-propanoic acid via CYP450-mediated ω-oxidation, followed by successive β-oxidation (44, 48). From there, metabolites can either be excreted via urine or enter enterohepatic circulation.

There is currently no information available on howavenanthramides are absorbed and metabolized; more research is needed to provide these important details.

**Bioavailability of Phenolics**

Bioavailability refers to the proportion of a nutrient that can be digested, absorbed, and metabolized—all processes a nutrient must undergo before it can enter general circulation (16). The most abundant phenolics in our diet are not necessarily those with the highest bioavailability. It is essential to investigate the metabolic fate of a phenolic after consumption to determine whether it is capable of providing beneficial health effects. The concentrations of intact and metabolized phenolics in plasma and urine after consumption represent direct evidence of their bioavailability.

Maximum plasma concentration ($C_{\text{max}}$), time to reach peak plasma concentration ($T_{\text{max}}$), and elimination half-life ($T_{1/2}$) are variables commonly used to measure and compare the bioavailability of different compounds.

**Table I. Major phenolic compound contents of common cereal grain flours (mg/kg)**

<table>
<thead>
<tr>
<th>Flour</th>
<th>Phenolic Acids</th>
<th>Alk(en)ylresorcinols</th>
<th>Avenanthramides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole grain rye</td>
<td>1,366</td>
<td>927</td>
<td>NA</td>
</tr>
<tr>
<td>Whole grain wheat</td>
<td>1,342</td>
<td>759</td>
<td>NA</td>
</tr>
<tr>
<td>White wheat</td>
<td>167</td>
<td>47</td>
<td>NA</td>
</tr>
<tr>
<td>Rice</td>
<td>197</td>
<td>ND&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td>Corn</td>
<td>601</td>
<td>ND</td>
<td>NA</td>
</tr>
<tr>
<td>Oat</td>
<td>470</td>
<td>ND</td>
<td>30–400</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data from Bratt et al. (9), Clifford (13), and Mattila et al. (43).
<sup>b</sup> NA = not applicable.
<sup>c</sup> ND = not detected; value below limit of quantification (3 mg/kg).

**Table II. Ferulic acid content of common cereal grains (μmol/100 g), by state**

<table>
<thead>
<tr>
<th>Grain</th>
<th>Free</th>
<th>Soluble Conjugate</th>
<th>Insoluble Bound</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat</td>
<td>0.57 ± 0.02</td>
<td>3.27 ± 0.27</td>
<td>329.06 ± 16.20</td>
<td>333.44 ± 16.20</td>
</tr>
<tr>
<td>Rice</td>
<td>0.70 ± 0.05</td>
<td>9.90 ± 0.34</td>
<td>142.80 ± 8.68</td>
<td>153.59 ± 8.68</td>
</tr>
<tr>
<td>Corn</td>
<td>0.92 ± 0.02</td>
<td>8.95 ± 0.11</td>
<td>896.27 ± 9.09</td>
<td>906.13 ± 9.09</td>
</tr>
<tr>
<td>Oat</td>
<td>0.65 ± 0.04</td>
<td>3.40 ± 0.56</td>
<td>180.61 ± 4.57</td>
<td>184.66 ± 4.61</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data from Al-Khudairy et al. (4).
showed two average maximum plasma concentrations after consuming 59 or 559.6 nM, respectively.

The bioavailability of ferulic acid, alk(en)ylresorcinols, and avenanthramides in wheat, rye, and oat bran, as determined in three different studies (11,27,30), is compared in Table III. These studies were selected because nonfermented cereal brans were the source of the phenolics studied. Based on the results, it appears that ferulic acid and avenanthramides take a similar length of time to reach $T_{\text{max}}$ and $T_{1/2}$. However, avenanthramides had a higher $C_{\text{max}}$ than ferulic acid, even when intake was lower. The $C_{\text{max}}$ values for alk(en)ylresorcinols were much higher than those for ferulic acid or avenanthramides, which was consistent with their slower rates of elimination. Based on these studies, alk(en)ylresorcinols appear to have the highest ferulic acid and the lowest bioavailability of the three phenolics. However, as discussed earlier, the antioxidant activity of alk(en)ylresorcinols is much lower than that of the other two phenolics.

Conclusions
Phenolics are a major contributor to the beneficial health effects of whole grains. One way that phenolics exert their effects is by acting as antioxidants; they scavenge ROS and prevent oxidative damage. To do this, however, they must first be absorbed and metabolized. The bioavailability of phenolics depends on factors such as the food matrix in which they are consumed, the compounds to which they are bound, the amount absorbed, their metabolic fate, and their excretion rate in urine.

When the beneficial effects of certain phenolics are evaluated, both antioxidant ability and bioavailability must be considered. Based on the available studies, the bioavailability of the three phenolics is ranked as alk(en)ylresorcinols > avenanthramides > ferulic acid, and antioxidant ability is ranked as avenanthramides > ferulic acid > alk(en)ylresorcinols. Because there are only a limited number of in vivo studies that have examined the antioxidant activities of these phenolics and their metabolites, full characterization of the bioavailability and bioactivity of these compounds is an area of great research interest.

References

Table III. Bioavailability of ferulic acid, alk(en)ylresorcinols, and avenanthramides in human studies (study sample size = 6)\(^a\)\(^b\)

<table>
<thead>
<tr>
<th>Phenolic Source</th>
<th>Amount Consumed (mg)</th>
<th>$T_{\text{max}}$ (hr) (\text{Mean} \pm \text{Range})</th>
<th>$C_{\text{max}}$ (nM) (\text{Mean} \pm \text{Range})</th>
<th>$T_{1/2}$ (hr) (\text{Mean} \pm \text{Range})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferulic acid Breakfast cereal (85% wheat bran)</td>
<td>260</td>
<td>2</td>
<td>1–3</td>
<td>150–210</td>
</tr>
<tr>
<td>Alk(en)ylresorcinols Rye bran</td>
<td>190</td>
<td>2.8 (^c)</td>
<td>1,253</td>
<td>6.7</td>
</tr>
<tr>
<td>Avenanthramides Out bran</td>
<td>118</td>
<td>1.5–2.3</td>
<td>559.6</td>
<td>2.0–3.2</td>
</tr>
<tr>
<td>Avenanthramides In bran</td>
<td>59</td>
<td>2.0–2.3</td>
<td>167.5</td>
<td>1.5–4.3</td>
</tr>
</tbody>
</table>

\(^a\) Data from Chen et al. (11), Kern et al. (27), and Landberg et al. (30).

\(^b\) $T_{\text{max}}$ = time to reach peak plasma concentration; $C_{\text{max}}$ = maximum plasma concentration; and $T_{1/2}$ = elimination half-life.

\(^c\) The plasma kinetic curves of alk(en)ylresorcinols have two peaks.


32. Lemperreur, I., Rouau, X., and Abecassis, J. Genetic and agronomic variation in arabinoxylan and ferulic acid contents of durum
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