

Plausible mechanisms for the protectiveness of whole grains^{1,2}

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ABSTRACT Dietary guidelines recommend the consumption of whole grains to prevent chronic diseases. Epidemiologic studies support the theory that whole grains are protective against cancer, especially gastrointestinal cancers such as gastric and colon cancer, and cardiovascular disease. Components in whole grains that may be protective include compounds that affect the gut environment, such as dietary fiber, resistant starch, and oligosaccharides. Whole grains are also rich in compounds that function as antioxidants, such as trace minerals and phenolic compounds, and phytoestrogens, with potential hormonal effects. Other potential mechanisms whereby whole grains may protect against disease include binding of carcinogens and modulation of the glycemic response. Clearly, the range of protective substances in whole grains is impressive and advice to consume additional whole grains is justified. Further study is needed regarding the mechanisms behind this protection so that the most potent protective components of whole grains will be maintained when developing whole grains into acceptable food products for the public. *Am J Clin Nutr* 1999;70(suppl):459S–63S.

KEY WORDS Cancer, gastric cancer, colon cancer, cardiovascular disease, diabetes, glycemic index, epidemiology, chronic disease prevention, whole grains, phytoestrogens, lignans, antioxidants, oligosaccharides, dietary fiber, trace minerals, vitamins, resistant starch, wheat, rice, corn

INTRODUCTION

Whole grains are important sources of many nutrients including dietary fiber, resistant starch, oligosaccharides, trace minerals, vitamins, and other compounds of interest in disease prevention, including phytoestrogens and antioxidants. Despite dietary recommendations to increase intake of whole grains, little research has been conducted on the physiologic effects of a diet high in whole grains. In general, mechanistic studies have been conducted by using the “magic bullet” approach in which one dietary ingredient is isolated and fed to either animals or human subjects. Thus, more published research supports a protective role for dietary fiber, trace minerals, vitamins, or other nutrients or phytochemicals than whole grains per se. Yet epidemiologic studies support the theory that fruit, vegetables, and whole grains are protective against a wide range of diseases (1, 2) and that this protection is generally greater than that seen with any isolated ingredient.

As described by Potter (3), if we were able to identify specific protective constituents, these would vary with the stage of the

cancer process and would also differ by sex, age, genetic and metabolic profile, and organ site. Potter suggested that the approach of focusing on nutritional magic bullets is much more problematic than encouraging a general increase in the consumption of plant foods. Feeding whole foods makes it difficult to isolate mechanisms, but such an approach ensures the built-in redundancy of multiple agents with independent, overlapping, and perhaps interactive mechanisms (3).

To defend the biological plausibility of a protective role for whole grains, this review first describes the components of whole grains that most likely protect against disease. Second, the important compositional differences between refined and whole grains are highlighted. Finally, the most likely biological mechanisms by which whole grains protect against cancer, cardiovascular disease, and diabetes are reviewed and supported.

WHAT ARE WHOLE GRAINS?

The major cereal grains include wheat, rice, and corn, whereas the minor grains include oats, rye, barley, triticale, sorghum, and millet (3). Wheat accounts for one-third of the total worldwide grain production and rice accounts for one-fourth. Generally, grains consumed in developed countries are subjected to some type of processing that may include milling, heat extraction, cooking, parboiling, or other techniques (4). Commercial cereals are usually extruded, puffed, flaked, or otherwise altered to make a desirable product for consumers.

Grain is composed of endosperm, germ, and bran. The endosperm comprises ≈80% of the whole grain, whereas the percentages accounted for by the germ and bran components vary among different grains. With the exception of rice, grains are high in dietary fiber, low in fat, have ≈10–15% protein, and are concentrated sources of starch, high in vitamins (especially B-vitamins), and good sources of minerals, particularly the trace minerals. In the milling process, the bran and germ are separated from the starchy endosperm and the latter is ground into flour. Nutrients and phytochemicals are not evenly distributed throughout the grain, with higher concentra-

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tions in the outer part of the grain, so refining results in reduced nutrient content.

COMPOSITIONAL DIFFERENCES BETWEEN WHOLE AND REFINED GRAINS

The known compositional differences between whole wheat and refined wheat are shown in **Table 1**. Whole grains contain no cholesterol, are low in fat, and are high in dietary fiber, starch, protein, vitamins, and minerals. Other components present in whole grains that have been associated with improved health status include lignans, tocotrienols, phenolic compounds, and anti-nutrients including phytic acid, tannins, and enzyme inhibitors. In the refining process, most of the bran and some of the germ are removed, resulting in loss of dietary fiber, vitamins, minerals, lignans, phytoestrogens, phenolic compounds, and phytic acid. Thus, refined grains have a higher starch content than do whole grains.

Although the structures of all grains are similar and include the endosperm, germ, and bran, the absolute amounts of each of these components vary among grains. For example, the bran amounts to 6% of corn and 16% of wheat. Important grains in the American diet include wheat, rice, corn, and oats. When the bran is removed in processing, associated substances are also likely to be removed. Phenolic acids, particularly the hydroxy-cinnamic acids known as ferulic acid and *p*-coumaric acid, are found in plant cell walls that generally link cellulose to other polysaccharide components. These compounds are thought to decrease the fermentability of dietary fiber (6). The total phenolic acid content of wheat, rice, and oat flours ranges from 71 to 87 $\mu\text{g/g}$, whereas that of maize flour is 309 $\mu\text{g/g}$ (7). Ferulic acid, *p*-coumaric acid, and syringic acid are the principal phenolic acids. Oats contain a number of lipid-soluble esters of caffeic and ferulic acids that function as natural antioxidants for the oat lipids. A recent study of phenolic acids in wheat flours found that ferulic acid was the most concentrated phenolic acid and that the more refined a flour is, the lower its phenolic acid content is (8).

TABLE 1
Compositional differences between whole and refined wheat¹

Component	Whole wheat	Refined wheat
Bran (%)	14	<0.1
Germ (%)	2.5	<0.1
Total dietary fiber (%)	13	3
Insoluble dietary fiber (%)	11.5	1.9
Soluble dietary fiber (%)	1.1	1.0
Protein (%)	14	14
Fat (%)	2.7	1.4
Starch and sugar (%)	70	83
Total minerals (%)	1.8	0.6
Selected minerals		
Zinc ($\mu\text{g/g}$)	29	8
Iron ($\mu\text{g/g}$)	35	13
Selenium ($\mu\text{g/g}$)	0.06	0.02
Selected vitamins		
Vitamin B-6 (mg/g)	7.5	1.4
Folic acid (mg/g)	0.57	0.11
Phenolic compounds		
Ferulic acid (mg^{-2}/g)	5	0.4
β -tocotrienol ($\mu\text{g/g}$)	32.8	5.7
Phytate phosphorus (mg/g)	2.9	0.1

¹Adapted from reference 5.

PROTECTIVE COMPONENTS IN WHOLE GRAINS

Fermentable carbohydrates

Whole grains are rich sources of fermentable carbohydrates including dietary fiber, resistant starch, and oligosaccharides. Undigested carbohydrate that reaches the colon is fermented by intestinal microflora to short-chain fatty acids and gases. Short-chain fatty acids include acetate, butyrate, and propionate; butyrate is a preferred fuel for the cells of the colonic mucosa. Short-chain fatty acid production has been related to lowered serum cholesterol and decreased risk of cancer (9). Undigested carbohydrates increase fecal wet weight and dry weight and speed intestinal transit.

No studies have examined the effects of whole grains on gut fermentation. Research has been conducted on grain components, including dietary fiber, resistant starch, and oligosaccharides. Oats, rye, and barley contain about one-third soluble fiber and two-thirds insoluble fiber. Soluble fiber is associated with cholesterol-lowering effects and improved glucose response, whereas insoluble fiber is associated with improved laxation. Wheat is lower in soluble fiber than most grains and rice contains virtually no soluble fiber. The refining process removes proportionally more of the insoluble fiber than the soluble fiber and refined grains are low in total dietary fiber.

Disruption of cell walls can increase the fermentability of dietary fiber. Coarse wheat bran has a greater fecal bulking effect than finely ground wheat bran when consumed at the same dosage (10), suggesting that the particle size of the whole grain is an important factor in determining the physiologic effect. Coarse bran delays gastric emptying and accelerates small bowel transit (11). The effects of coarse bran are similar to the effects of inert plastic particles, suggesting that the coarse nature of whole grains compared with refined grains has a unique physiologic effect beyond the differences in composition between whole and refined grains.

Several mechanisms have been proposed to explain the protective action of dietary fiber. Increased fecal bulk and decreased transit time allow less opportunity for fecal mutagens to interact with the intestinal epithelium. Secondary bile acids are thought to promote cell proliferation, thereby providing more opportunities for mutations to occur and for abnormal cells to replicate. The effect of fiber on the actions of bile acids may be attributable to the binding or diluting of bile acids. Fermentation of dietary fiber results in production of short-chain fatty acids, which lowers intestinal pH; this in turn inhibits the conversion of primary bile acids to secondary bile acids. At low pH, the solubility of free bile acids is reduced, diminishing their availability for cocarcinogenic activity. Fermentation of dietary fiber results in production of butyrate, a short-chain fatty acid that has been shown to be antineoplastic (12).

The results of animal studies concerning dietary fiber have been inconsistent. Potential reasons for this inconsistency include the different types of fiber fed to animals, differences among species, use of different tumor-inducing agents, and use of unphysiologic amounts of dietary fiber or carcinogens in the experiments (13). Wheat bran was the type of fiber most consistently shown to inhibit carcinogenesis.

It is now accepted that not all starch is digested and absorbed during gut transit. Factors that determine whether starch is resistant to digestion include the physical form of grains or seeds in which starch is located, particularly whether these are whole or partially disrupted; the size and type of starch granules; associa-

tions between starch and other dietary components; and cooking and food processing, especially heating and cooling (6). Because the starch in whole grains is apparently more resistant to digestion than refined starch, whole grains should improve the gut environment.

Consumption of whole foods is also known to slow the digestion and absorption of carbohydrates. Studies showed that postprandial blood glucose and insulin responses were greatly affected by food structure (14). Any process that disrupts the physical or botanical structure of food ingredients increases the plasma glucose and insulin responses. Food structure was found to be more important than gelatinization or presence of viscous dietary fiber in determining glycemic response in one study (15). Another study showed that preserving the structure of foods was an important determinant of glycemic response in patients with type 2 diabetes (16). Consumption of refined grains tends to increase glycemic response, and therefore consumption of whole grains should reduce glycemic response (17).

Intact whole grains of barley, rice, rye, oats, corn, buckwheat, and wheat have glycemic indexes of 36–81, with barley and oats having the lowest values (18). Lower blood glucose concentrations and decreased insulin secretion were measured in subjects with and without diabetes mellitus who consumed a low-glycemic-index (=67) diet containing pumpernickel bread with intact whole grains, bulgar (parboiled wheat), pasta, and legumes compared with subjects who consumed a high-glycemic-index (=90) diet containing white bread and potato (18).

In addition to dietary fiber and resistant starch, grains contain significant amounts of oligosaccharides. Oligosaccharides are defined as carbohydrates with a low (2–20) degree of polymerization. Common oligosaccharides include oligofructose and inulin. Wheat flour contains from 1% to 4% fructan on a dry-weight basis (19). Fructans have also been found in rye and barley, with very young barley kernels containing 22% fructan (19). Van Loo (19) estimated that 78% of the North American intake of oligosaccharides is from wheat.

Oligosaccharides are thought to have effects similar to those of soluble dietary fibers in the human gut. In addition, studies consistently found that oligosaccharides were able to alter the human fecal flora. Many human studies found that consumption of fructooligosaccharides increased bifidobacteria in the gut while decreasing concentrations of *Escherichia coli*, clostridia, and bacteroides (20, 21).

Fat and associated substances

Although grains are low in fat, they have a favorable fatty acid composition consisting primarily of oleic and linoleic acids. Furthermore, grains are rich in other compounds such as the tocotrienols, plant sterols, and oryzanol, which were found to have hypocholesterolemic effects in animal studies (22). β -Sitosterol in grains was found to reduce the incidence of tumors in rats (23).

Antioxidants

Antioxidants are compounds that delay the onset of oxidation or slow the rate at which oxidizable substrates are oxidized. Whole grains contain many antioxidants, including vitamins; trace minerals; nonnutrients such as phenolic acids, lignans, and phytoestrogens; and antinutrients such as phytic acid (24). Whole grains are concentrated sources of vitamin E, especially tocotrienols. Whole grains are also rich sources of selenium,

although the selenium content of grains varies according to the composition of the soil. Trace minerals such as copper, zinc, and manganese are also concentrated in the outer layer of grains; therefore, milled grains are poor sources of trace minerals.

Grains are thought to be particularly rich sources of phenolic acids, which are located in the bran layer. Durum wheat bran was shown to have antioxidant activity in an in vitro model (25). Of the phenolic acids in wheat bran, ferulic acid had the highest concentration. The potentially anticarcinogenic mechanism of phenolic compounds involves the induction of detoxification systems, specifically the phase II conjugation reactions. Wattenberg (26) classified caffeic and ferulic acids as inhibitors that act in 2 ways, by 1) preventing the formation of carcinogens from precursor compounds, and 2) blocking the reaction of carcinogens with critical cellular macromolecules.

Phytic acid, which is concentrated in grains, is a known antioxidant (27). Phytic acid forms chelates with various metals, which suppress damaging iron-catalyzed redox reactions (28). Colonic bacteria produce oxygen radicals in appreciable amounts; dietary phytic acid may suppress oxidant damage to the intestinal epithelium and neighboring cells.

Vitamin E is another antioxidant present in whole grains that is removed in the refining process. Vitamin E is an intracellular antioxidant that protects polyunsaturated fatty acids in cell membranes from oxidative damage. Another possible mechanism for vitamin E relates to its capacity to keep selenium in the reduced state. Vitamin E inhibits the formation of nitrosamines, especially at low pH. Wattenberg (26) characterized vitamin E as a cancer inhibitor that exerts its effect by preventing the formation of carcinogens from precursor compounds. It was shown that in a rat model, the bioavailability of vitamin E in breakfast cereal was good (29). Taken as a whole, the results of animal experiments on the effect of dietary vitamin E in cancer prevention have been inconclusive.

Selenium is another compound that is removed in the refining process. The amount of selenium found in grain is proportional to the selenium content of the soil in which the grain was grown. Selenium functions as a cofactor for glutathione peroxidase, an enzyme that protects against oxidative tissue damage. Wattenberg (26) classified selenium as a suppressing agent, or inhibitor, that prevents the expression of neoplasia in cells that have been exposed to a carcinogen previously.

Lignans and phytoestrogens

Hormonally active compounds in grains called lignans may protect against hormonally mediated diseases (30). Lignans are compounds with a 2,3-dibenzylbutane structure that exist as minor constituents of many plants, where they provide the building blocks to form lignin in the plant cell wall (31). The plant lignans secoisolariciresinol and matairesinol are converted by human gut bacteria to the mammalian lignans enterolactone and enterodiol. Limited information is available on the concentrations of lignans and their precursors in food. Because of the association between fiber intake and lignan excretion, it is assumed that plant lignans are contained in the outer layers of the grain. A recently published table (32) supports the theory that whole grains and the bran layer of grains are concentrated sources of lignans; these concentrated sources include whole-grain wheat, whole-grain oats, and rye meal. Seeds are also concentrated sources of lignans. Of the seeds, the most concentrated source is flaxseed, and other good sources are pumpkin seeds,



TABLE 2
Selected components in whole grains and their postulated mechanisms¹

Component	Antioxidant	Tumor growth suppressor	Enzyme modulator	Binding scavenger	Chemical inactivator	Cholesterol-lowering	Gut modifier	Hormonal effects
Dietary fiber			✓			✓	✓	✓
Oligosaccharides			✓	✓		✓	✓	
Flavonoids	✓	✓	✓					
Inositols	✓							
Lignin	✓							
n-3 Fatty acids		✓				✓		
Phenolics	✓	✓	✓					
Phytates	✓							
Phytoestrogens	✓	✓						✓
Protease inhibitors		✓						
Saponins		✓						
Selenium	✓	✓						
Terpenoids								
Tocopherols	✓		✓					
Zinc	✓				✓			

¹ From references 2 and 37.

caraway seeds, and sunflower seeds. These compositional data suggest that eating whole-grain breads and cereals is the best way to obtain lignans in the diet.

Grains and other high-fiber foods increase urinary lignan excretion, which can serve as an indirect measure of the lignan content of foods (33). Mammalian lignan production from plant foods was studied by Thompson et al (34) who used an in vitro fermentation method with human fecal microbiota. Oilseeds, particularly flaxseed flour and meal, produced the highest concentrations of lignans, followed by dried seaweeds, whole legumes, cereal brans, whole-grain cereals, vegetables, and fruits. The concentration of lignans produced from flaxseed was \approx 100 times greater than that produced from most other foods.

Differences in the metabolism of phytoestrogens among individuals have been noted. Adlercreutz et al (33) found that total urinary lignan excretion in Finnish women was positively correlated with total fiber intake, total fiber intake per kg body weight, and grain fiber intake per kg body weight. Similarly, the geometric mean excretion of enterolactone was positively correlated with the geometric mean intake of dietary grain products (kcal/d) of 5 groups of women ($r = 0.996$) (33).

Given the association of lignan excretion with fiber intake, plant lignans are probably concentrated in the outer layers of the grain. Because current processing techniques eliminate this fraction of the grain, lignans may not be found in processed grain products on the market and would only be found in whole-grain foods. Recently, Thompson et al (35) found significant differences in the lignan content of flaxseed depending on the variety, harvest location, and harvest year; this suggests that extensive analysis of the lignan content of whole grains is warranted.

Lignans have a diphenolic structure similar to that of estrogenic compounds, which has created interest in a possible estrogenic function for these compounds. Consumption of certain plants is known to alter fertility. Over 300 plants have been identified as having the ability to initiate estrus in animals. Limited data from animal studies support the hypothesis that there is a relation between phytoestrogens and sex steroid action. However, little is known about the biological and physiologic effects of phytoestrogens in humans. Whether phytoestrogens have an estro-

genic or antiestrogenic effect may depend on the amount of endogenous estrogens present. Our group found that consumption of flax powder (10 g/d) increased the average luteal phase length of the menstrual cycle in premenopausal women (36). Any significant increase in the overall cycle length would be potentially beneficial in lowering the risk for hormone-dependent cancers.

Antinutrients

Antinutrients found in grains include digestive enzyme (protease and amylase) inhibitors, phytic acid, hemagglutinins, phenolic compounds, and tannins. Protease inhibitors, phytic acid, phenolic compounds, and saponins were shown to reduce the risk for cancers of the colon and breast in animals. Phytic acid, lectins, phenolic compounds, amylase inhibitors, and saponins were also shown to lower one or more of the following substances in plasma: glucose, insulin, cholesterol, and triacylglycerol (13).

In grains, protease inhibitors make up 5–10% of the water-soluble protein and are concentrated in the endosperm and embryo. According to Wattenberg (26), protease inhibitors have inhibitory actions including both suppression of the expression of neoplasia in cells already exposed to a carcinogenic agent and inhibition of tumor promotion.

OTHER POTENTIAL MECHANISMS


Because of the complex nature of whole grains, many other potential mechanisms may be responsible for the protective properties of whole grains. Components in whole grains may bind carcinogens and thereby limit absorption by or contact with the gut.

Whole grains are also rich sources of a wide range of phytochemicals with anticarcinogenic properties (37) (Table 2). These phytochemicals include agents that block initial DNA damage and agents that suppress postinitiation processes. Many of the phytochemicals concentrated in grains have shown promising results in experimental studies. Yet it is important to remember that grains, or any other foods, are not eaten in isolation and results from cell culture studies or animal studies in which high concentrations of phytochemicals were used may not be relevant to overall dietary guidance.

POTENTIAL ADVERSE EFFECTS OF WHOLE GRAINS

Whole grains may reduce the availability of minerals because of the mineral-binding abilities of fiber and phytic acid. Refined grains have lower fiber and phytate contents but also lower mineral contents. Consumption of fiber and whole grains in recommended amounts (20–35 g/d for fiber and 3 servings/d for whole grains) have not been found to have any adverse effects on mineral status.

CONCLUSIONS

Whole grains are rich in many components, including dietary fiber, starch, certain fatty acids, antioxidant nutrients, minerals, vitamins, lignans, and phenolic compounds, that have been linked to reduced risk for coronary artery disease, cancer, diabetes, obesity, and other chronic diseases. Most of these components are found in the germ and bran, which are reduced in the grain-refining process. The most potent protective components of whole grains need to be identified so that efforts can be directed toward minimizing the loss of physiologically important constituents of grains during processing. Efforts to educate the public about increasing the intake of whole grains to recommended amounts are also needed. 

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