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Whole Grains from a Mechanistic View

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Wheat, rice, and corn are the most widely eaten whole grains, followed by oats, rye, and barley. A wheat kernel consists of 80–85% endosperm, 10–14% bran, and 2.5–3% germ (Figure 1). Whole grains contain a high amount of bioactive substances such as fiber, vitamins, minerals, antioxidants, and other phytochemicals such as betaine, choline, sulfur amino acids, and melatonin, which account for at least 15% of the whole grain by weight. Most bioactive substances are in the bran (about 52% by weight) and the germ (at least 24% by weight) fractions. In refined cereals, the levels of bioactive compounds are substantially reduced due to the complete or partial removal of the germ and bran fractions.

The Physiological Mechanisms Involved as Unraveled via the Reductionist Approach

Epidemiological research indicates that consumption of whole grain products significantly protects against obesity (3), type 2 diabetes (6), cardiovascular disease (4), and some cancers (2), especially within the digestive tract, the effect being the most conclusive against type 2 diabetes. How do whole grain foods offer protection against these chronic diseases? To answer this question, the reductionist approach has been privileged up until today and has allowed the unraveling of several mechanisms at the basis of how whole grain cereals protect health. This approach mainly consists in relating the effect of whole grains on one bioactive compound with one physiological effect.

Human intervention studies have notably shown that increased whole grain product consumption may contribute to improved intestinal health, a lower BMI (body mass index), a healthier blood lipid profile, improved blood glucose control, increased insulin sensitivity, lower homocysteine levels (a cardiovascular risk factor), and reduced inflammatory markers. The preservation of an intact food structure (i.e., more or less intact cereal kernels) may also lead to an increased feeling of satiety that is important in weight management. Whole grain products are also generally a rich source of fiber, antioxidants, anticarcinogens, and magnesium, which are all potentially protective. In addition, whole grain products may lead to increased butyrate production (protective against tumor growth) within the colon due to resistant starch (the starch fraction that is not digested in the small intestine) and fiber fermentation. Some antinutrients like phytic acid, lectins, tannins, saponins, and inhibitors of enzymes (e.g., proteases and α-amylases) may also positively affect starch hydrolysis rate and subsequent blood glucose levels. Finally, it is now well-demonstrated that the consumption of low-GI (glycemic index) whole grain products either at dinner or at breakfast positively influence the glycemia (or blood glucose control) at the following meal ("the second-meal" effect), an effect which may contribute to the long-term metabolic benefits of low-GI diets.

Besides these quite well-known mechanisms, a whole grain also contains a multitude of other bioactive substances. The content of some bioactive substances may however seem too low for reaching a significant effect. But it becomes increasingly obvious that the combination of all these bioactive substances might have positive synergistic health effects, not only within the intestine or towards cardiovascular diseases, glucose metabolism, and weight regulation, but also in new areas such as bone health and mental health (Figure 2). Let's now have a detailed look at the main physiological effects of whole grain bioactive compounds.

Whole Grain Cereals as a Rich Source of Fiber. Whole grains are primarily a rich source of fiber. The fiber content of whole wheat varies between 9 and 17 grams per 100 grams. That is more than vegetables, which usually have up to 6 grams per 100 grams edible portion.

Wheat fiber is mainly insoluble fiber and resistant starch. Fibers from whole grain foods are beneficial to gut health. Insol-

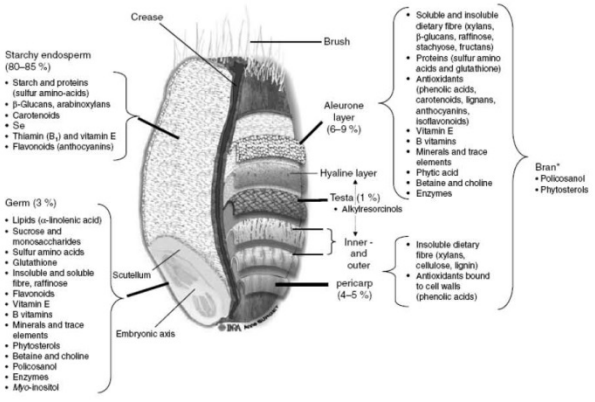

Fig 1. The three wheat fractions (bran, germ, and endosperm) with their main bioactive compounds; whole grain wheat has a heterogeneous structure with bioactive compounds unevenly distributed within its different parts.

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uble fiber, which is poorly fermented in the colon, favors an increased transit time and greater fecal bulking, two parameters that probably prevent colon cancer by diluting carcinogens and reducing their time in contact with epithelial cells. Cereal fibers also increase satiety and help control body weight. Fiber fermentation is also associated with a high production of short chain fatty acids (e.g., butyrate) that are associated with a lower risk of cancer, favoring the development of a healthy colonic microbiota (i.e., a prebiotic effect). However, the way the fiber may be beneficial for human health is multifactorial and it involves other physiological mechanisms, e.g., hormonal effects or decreased gastric emptying rate (due to viscous fiber).

Whole Grain Cereals as Rich Sources of Anticarcinogenic Compounds. This anticarcinogenic effect is mainly attributed to the antioxidant and anti-inflammatory properties of several bioactive compounds, as increased oxidative stress and inflammation are involved in cancer etiology. Phenolic acids, flavonoids, carotenoids, vitamin E, *n*-3 fatty acids, lignan phytoestrogens, steroid saponins (found mainly in oats), phytic acid, and selenium are all potential suppressors of tumor growth, but human, animal, and *in vitro* cell studies indicate that their mechanisms of action may differ. To summarize, it is possible to distinguish between the anticarcinogenic effects of insoluble fiber (including lignin) and phytochemicals. Insoluble fiber may act directly by absorbing or diluting carcinogens (through increased fecal bulk by water absorption) or indirectly by decreasing colon pH (through SCFA production) and increasing butyrate production. The role of phytochemicals is complex, multifactorial, and notably involves their antioxidant properties.

Whole Grain Cereals as a Rich Source of Magnesium and Antioxidants. Not only do whole grains contain fiber, but also relevant amounts of magnesium and antioxidants. The high magnesium content may partly explain the beneficial effect of whole grain foods on insulin sensitivity and risk of type 2 diabetes. Magnesium increases insulin secretion and it is known that diabetes is often associated with a lack of magnesium. In a whole grain there are also different substances that contribute directly or indirectly to protect the body from increased oxidative stress. At least 30 bioactive compounds might be involved, such as polyphenols, carotenoids, vitamin E, minerals (e.g., selenium, iron, copper, and zinc, which act as a cofactor in antioxidant enzymes), and sulfur-containing amino acids (i.e., methionine and cystine that are precursors of glutathione, an endogenous antioxidant). Even lignin, generally considered biologically inactive, has been shown to exert a potential antioxidant effect in animals. Antioxidants found in whole grains may also protect the intestinal epithelium against damage by free radicals, such as those produced within the colon through bacteria metabolism. The antioxidants in whole grain cereals may therefore act via different, complex, and synergetic mechanisms *in vivo*. However, the antioxidant action of whole grain cereals has not yet been convincingly validated in humans and requires further exploration.

Other Bioactive Compounds and Potential Health Effects. Recent findings, the exhaustive listing of bioactive compounds found in whole grain wheat, their content in whole grain, bran, and germ fractions, and their estimated bioavailability have led to new hypotheses (1). The involvement of polyphenols in cell signaling and gene regulation and of sulfur compounds, lignin, and phytic acid should be considered in antioxidant protection. Whole grain wheat is also a rich source of methyl donors/lipotropes (methionine, betaine, choline, inositol, and folates) that may be involved in cardiovascular/hepatic protec-

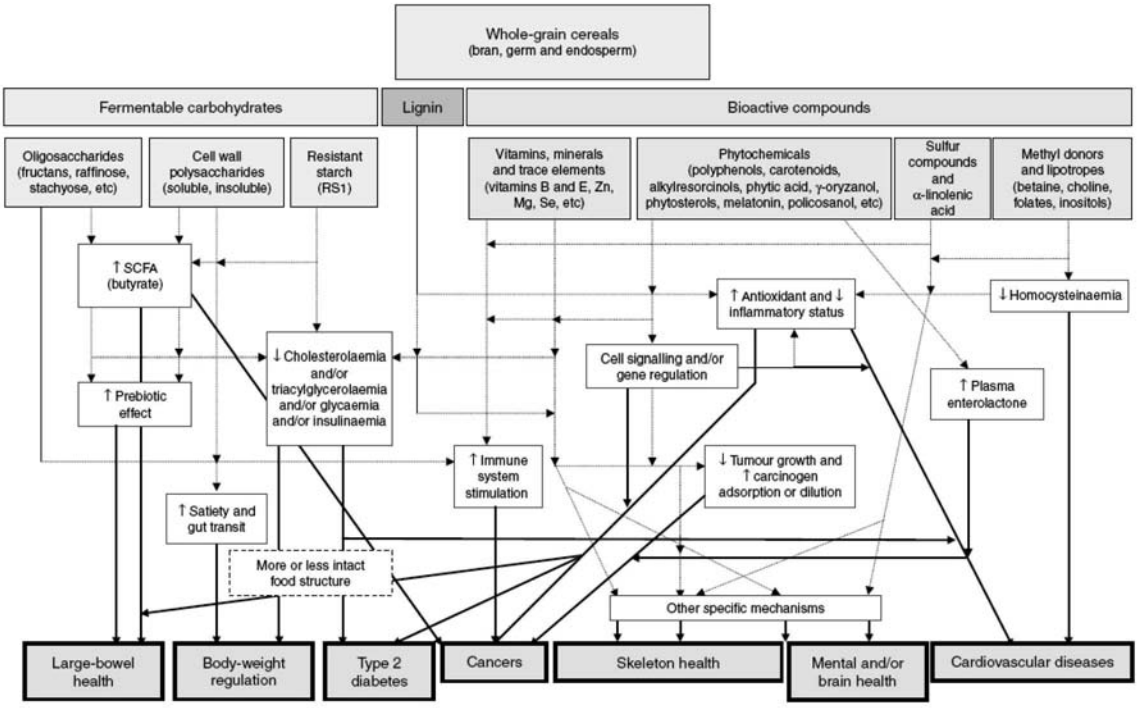

Fig 2. Current and new proposed physiological mechanisms involved in protection by whole grain cereals. The dotted thin arrows indicate the link between whole grain bioactive compounds and protective physiological mechanisms, while the colored plain arrows indicate the relationship between physiological mechanisms and health outcomes.

tion, lipid metabolism, and DNA methylation. Potential protective effects of bound phenolic acids within the colon, of the B-complex vitamins on the nervous system and mental health, of oligosaccharides as prebiotics, of compounds associated with skeleton health (e.g., phosphorous, calcium, magnesium, manganese, copper, and vitamin K), and of other compounds such as α-linolenic acid, policosanol, melatonin, phytosterols, and *para*-aminobenzoic acid also deserve to be increasingly studied. For example, it would be particularly interesting to study the effect of whole grain products on mental health issues like depression (5), insomnia, and cognitive decline given that other bioactive compounds, such as choline, ferulic acid, magnesium, zinc, copper, inositols, policosanol, and melatonin, are also potential candidates for mental health protection and equilibrium.

Considering the Whole Grain Package: A More Integrative and Holistic Approach

The contents of individual bioactive compounds in whole grain may seem too low for them to have any significant or lasting physiological effects. It is becoming more and more evident that the synergetic action of several bioactive compounds contributes to protecting health and the maintenance of one physiological function, not just one compound. Figures 1 and 2 illustrate this concept of "whole grain package." Therefore, obesity and body weight regulation, cardiovascular diseases, type 2 diabetes, cancers, and gut, mental/nervous system, and skeleton health problems might be potentially prevented by at least 10, 34, 17, 32, 10, 26, and 16 different bioactive compounds or groups of compounds respectively (1).

Until today, research has tended to focus on the study of the isolated effects of individual bioactive compounds based on a reductionist approach. The combined physiological effects of the bioactive compounds would be now much more interesting to investigate based on a more integrative and holistic approach, but this is probably more difficult to apprehend. Today, the development of metabolomics and nutrigenomics offers new opportunity to further study such combined and complex effects. With these new techniques, nutrition looks at the impact on the genes, protein synthesis, and metabolic pathways in body biofluids and cells following whole grain based diet consumption in humans. In the end, due to the gap between observational studies and the elucidation of the causal physiological mechanisms involved, there is a real need to lead intervention studies with complex whole grain products in humans.

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