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Rachana Poudel
University of Nebraska - Lincoln, rpoudel2@huskers.unl.edu

Madhav Bhatta
University of Nebraska - Lincoln, madhav.bhatta@huskers.unl.edu

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Review of Nutraceuticals and Functional Properties of Whole Wheat

Rachana Poudel[1]* and Madhav Bhatta[2]

[1]*Food Science and Technology Department, University of Nebraska-Lincoln, Lincoln, USA*
[2]*Department of Agronomy and Horticulture, University of Nebraska-Lincoln, Lincoln, USA*

Abstract

Wheat (*Triticum aestivum* L.) is one of the most commonly cultivated and consumed cereals throughout the world. Though phytochemicals and antioxidants in the cereal grains have not been studied as in fruits and vegetables, given the role of wheat in our diet plate, it is a given of primary importance to understand the chemistry of our major food, wheat. The presence of diverse polyphenols and their action against leading cause of death, including heart diseases, cancer, obesity, and diabetes, widens the scope of wheat. Phytochemicals such as phenolic acids, alkylresorcinols, flavonoids, phytosterols, and carotenoids are present in whole wheat. The majority of phytochemicals are located in the wheat bran/germ fraction, and they are the leading contributors to the health promoting activities. However, the presence of anti-nutrients and binding of phenolic acids with protein may have adverse effect on health. This review mainly focuses on studies that have been carried out in the past decade to present, emphasizing the importance of whole wheat and whole wheat based products in preventing major diseases and disease conditions, potentials threats, current lacks, and future prospects.

Keywords: Phytochemicals; Wheat; Polyphenols; Antioxidants; Anti-nutrients

Introduction

Wheat (*Triticum* spp.) is an ancient grain and also one of the leading cereal crops, ranking third, in the world [1]. The centre of origin of wheat is South-western Asia. Hybridization of diploid and tetraploid wheat occurred several thousand years ago resulting in the production of hexaploid wheat (common wheat: *T. aestivum* L.) [2]. Common wheat has been consumed as a food for more than 12,000 years. It was believed that Greek, Roman, Sumerian, and Finnish mythology had god and goddesses of wheat. In the United States, wheat was introduced in the early colonial years. However, it was not until 19^{th} century that wheat cultivation flourished, which was brought by the Russian immigrants who settled in the Kansas [2]. At present, the largest commercial producers of wheat include China, India, United States, Russian Federation, and France [1].

The unique viscoelastic properties of wheat, which allow the formation of a number of products, make it leading choice on our diet plate [3]. The ability of wheat to be well suited for a wide range of agro-climatic zones make it the most cultivated crop throughout the world and in the United States. These two reasons make wheat the largest produced and consumed cereals throughout the world. In the U.S., wheat is grown as winter and spring wheat: winter wheat accounts for 70-80% of total production in the U.S. [4]. The United States Department of Agriculture (USDA) classified wheat as hard red winter wheat, hard red spring wheat, soft red winter wheat, white wheat, and Durum wheat, the use of which may be different depending upon the final product. The composition of wheat varies among genotypes, environment and their interactions, classes of wheat [5], and parts of a wheat grain [6]. A wheat grain is divided into three main parts, the bran, endosperm, and germ. The bran, the outer layer, is composed of fibres (50%), antioxidants, B vitamins, and 50-80% of minerals are composed of iron, copper, zinc and magnesium [7]. Wheat is also a rich source of protein, carbohydrates and fibres as mentioned in several previous studies [3]. The protein content in the germ and aleurone layer is 30%, whereas the pericarp layer contains 10% of the total protein [6]. Though protein contents in wheat aleurone and germ layer are high, the contribution of endosperm to total kernel protein content is relatively higher; about 74% [6].

The health promoting effects of whole wheat or whole wheat based products are mainly due to the presence of phytochemicals in wheat, including phenolic, carotenoids, lignans and vitamin E [8]. Each of these phytochemicals in combination or alone accelerates health-promoting events. Several past studies have shown the effectiveness of polyphenols against oxidative stress and dietary fibre against cancer [9]. The amount of these phytochemicals varies depending upon the fraction of wheat grain and the processing conditions. In a study, environment influences on the total phytochemical concentrations were pronounced more significant than production system [9]. In the recent years, several studies on health benefits of whole wheat are increasing the perception of people and inclination towards whole wheat/whole wheat based products. Due to the association of whole wheat in preventing several diseases, numerous studies have been carried out to date with no sign of decreasing. In future, oxidative stress-related diseases, obesity, cancer, and diabetes are likely to cause large number of deaths. Though several studies have been conducted and much is known about benefits of whole wheat, there remains a lack of information about the phytochemicals present in whole wheat to their possible association with different diseases. This paper reviews phytochemicals present in whole wheat and studies of several health benefits and the health promoting action of whole wheat with special emphasis on oxidative stress, heart diseases, cancer, inflammation, obesity, and immunology carried out in the last decade.

Composition of Whole Wheat

Wheat grain is comprised mainly of starch, proteins, and cell wall polysaccharides (dietary fibre) [5]. These components in combination

***Corresponding author:** Poudel R, Graduate Research Assistant, Food Science and Technology Department, University of Nebraska-Lincoln, Lincoln, NE 68588, USA, Tel: 405-474-8139; E-mail: rpoudel2@huskers.unl.edu

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account for 90% of the grain composition on dry weight basis. The minor components present in wheat are lipids, terpenoids, phenolics, minerals, and vitamins. The fat soluble nutrients that include vitamin E (tocopherols and tocotrienols, collectively called as tocols) and the carotenoids are located in wheat flour. In the wheat kernel, tocols are unevenly distributed as the activity of methyltransferases is crucial in determining the relative proportion of vitamins in grains [6]. Tocols scavenge peroxyl radicals, singlet oxygen and nitrogen oxide, which are responsible for the oxidative stress-mediated diseases, such as cancer and coronary heart diseases. However, the bran matrix formed in whole wheat flour may decrease the bioavailability of tocols [8]. According to the U.S. Department of Agriculture's National Nutrient Database, whole-grain wheat flour has 0.71-0.85 mg/g of vitamin E (α-tocopherol). Processing of the whole wheat causes loss of tocols, as they are subjected to oxidation in the presence of heat, light or alkali. During extrusion, around 85% losses of tocols have been reported [9]. Carotenoids are not active as alone but contribute to antioxidant property of wheat [10]. Lutein, β-cryptoxanthin, zeaxanthin (xanthophyll: hydroxylated carbons) and β-carotene (hydrocarbon) is the carotenoids present in wheat [9]. Though wheat flour is not a rich source of carotenoids, it is still an important nutrient considering the amount of whole wheat consumed.

The phytosterols are mainly located in the wheat kernel [9]. The total phytosterols in winter wheat grain range from 0.62-0.96 mg/g dry weight basis [7]. The predominant phytosterol in wheat is the desmethyl sterols (no methyl group at C-4). Campesterol, sitosterol, stigmasterol, avenasterols (desmethyl sterols) and the stanols (saturated sterols) are different phytosterols that have been reported in wheat grains. Phytosterols have been shown to reduce low-density lipoprotein cholesterols and may have a promising effect against cancer [8].

Phenolics, compounds containing a phenol ring and at least one hydroxyl substituent, are the main constituents of wheat. Phenolic compounds are located mainly in the outer barn layers of kernels [7]. Wheat phenolics include the phenolic acids, flavonoids, and alkylresorcinols. Ferulic acid (main phenolic acid in wheat), caffeic acid, sinapic acid, protocatechuic acid, vanillic acid, p-hydroxybenzoic acids, p-coumaric acid, and syringic acid are some phenolic acids present in wheat bran and whole wheat flour [9]. Phenolic acids are mainly known for their antioxidative properties. However, the antioxidative properties of phenolic acids have been reported to decrease when they bind to the protein. The flavonoids are mainly located in the wheat germ (0.09 μmol/g of grain) [11]. Flavonoids have both anti-oxidative and anti-inflammatory activities [12]. Lastly, lignans are the phytoestrogens, which are found in the wheat bran. Though studies remain limited on wheat lignans, their association has been reported against cancer [13].

Oxidative Stress

High reactive molecules, known as free radicals, are produced in our body that causes oxidative stress (imbalance between oxidants and antioxidants) due to the hyper oxidation nature of oxygen [14]. When our body can't cope with the oxidative stress, oxidative damage occurs in the form of many diseases, including but not limited to Coronary Heart Diseases (CHD), cancer and diabetes [14]. However, the regular intake of whole wheat in our diet has been associated with the reduced risk of chronic diseases and oxidative stress related disorders [11]. Several mechanisms that include termination of free radical-mediated oxidative reactions, stimulation of antioxidant enzymes, reduction of peroxides, and chelation of transition metals, are exhibited by dietary antioxidants/polyphenols against the oxidative stress [15]. The beneficial effects of whole wheat are associated with the presence of phenolic, carotenoids, vitamin E, lignans, polysterols and dietary fibre.

Ferulic acid, the main phenolic acids in wheat, has high anti-oxidative activity [16]. For example, several studies have shown its protective properties against cancer, skin diseases, and diabetes [7]. The pericarp, testa, and aleurone layer of wheat contain the highest concentration of polyphenols. Several studies have been conducted to date to show that the polyphenols in wheat and their ability to reduce oxidative stress-mediated disease [17]. In the current years, the focus has been made on identifying the specific effect of wheat components (different polyphenols) in reducing the risk of diseases.

Cancer

Cancer is the second leading disease causing the death of people in the United States after heart disease (Figure 1) [18]. The expression of different types of cancers partially reflects different environmental hazards and lifestyles. For instance, mouth, oesophagus, and stomach cancer are associated with environments lacking good hygiene, foods and food preservation systems, whereas colorectal cancer and breast cancers are closely associated with westernized cultures [19]. Whole wheat is a rich source of dietary fibres that include a non-starch polysaccharide, resistant starches, sugar alcohols, and oligosaccharides. It has been shown that oligosaccharide alone or in combination with probiotics significantly reduced colonic aberrant crypt foci and tumors induced azoxymethane [20]. Resistant starches shown in the whole wheat improved a number of bowel health markers, including increased butyrate [21]. These resistant starches escape digestion and undergo fermentation in the colon to provide a significant amount of short chain fatty acids including butyrate. Butyrate exerts its antineoplastic effect by modulation of gene expression, inhibition of cell growth, increased histone acetylation, and induced apoptosis [22]. Other fermentative activities and short chain fatty acids improve the availability and uptake of cations, such as calcium and magnesium by their opening influence on tight junctions in the colonic epithelium [23]. Lack of fermentation in the large bowel by the usage of antibiotics diminish butyrate and the production of the B vitamins, which otherwise are beneficial in cancer prevention [23].

Phytosterols, phenolics, and selenium shown in whole wheat have anticancer effects [24]. Some compounds act as antioxidants, locking up minerals and trace element capable of producing free radicals from fats [24]. Phenolics present in the whole wheat can act as antibiotics or antioxidants. The presence of the orthophenolics in wheat was correlated significantly with tumour inhibition [25]. The metabolism of lignans (di-phenolics found in whole wheat) has been also been correlated with a reduced risk of breast cancer [26]. Dimethyl benzoquinone (found in wheat germ) was shown to be effective as an anticancer agent in the rodent colon cancer model at low concentrations [27]. Selenium, present in the aleurone layers and germ of wheat, (1-2 ppm) was effective in cancer prevention using the rodent colon cancer model [28]; however, no beneficial effects occurred in older individuals when they were supplemented with dietary Se [29]. An anticancer bio peptide, Lunasin (249.2 μg luanisn/g seed) in wheat was reported [30]. Anti-carcinogenic properties of lunasin were previously reported in soybean [31]. The anti-carcinogenic activity of Lunasin was attributed to its ability to bind to deacetylated histones in the nucleus. According to the study, Lunasin selectively killed the cells that disrupted histone acetylation-deacetylation balance, when oncoprotein inactivates Rb (tumor suppressor). Inactivation of Rb dissociated with the Rb-histone deacetylase complex and this exposure provided a site for lunasin bonding. This binding caused cell death of the transformed cells

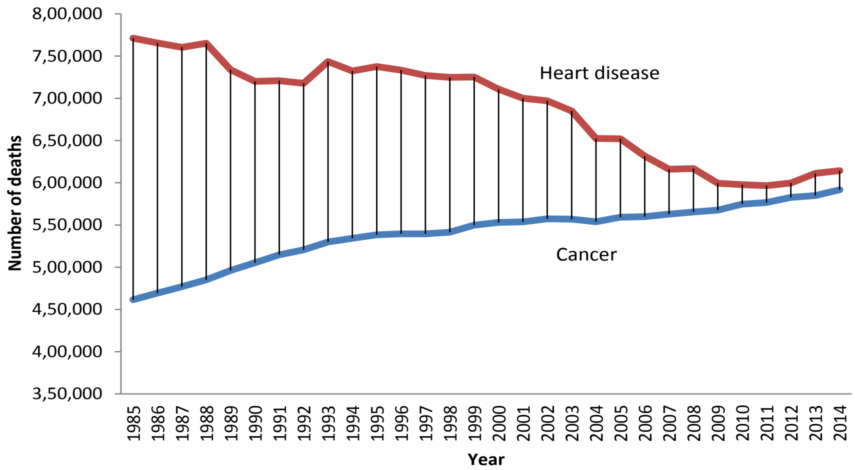

Figure 1: Number of deaths due to heart disease and cancer in the United States from 1985 to 2014. Source: CDC: NCHS, National vital statistics system, mortality.

(cells that were being transferred by disrupting histone acetylation-deacetylation) only.

Wheat extracts also inhibited human colon cancer *in vitro* [15]. The percentage inhibitions of cancer cells were correlated with percentage composition of soluble ferulic acid and p-coumaric acid. Immature wheat kernels were more effective against two colon cancer cell lines (HT-29 and Caco-2) and HeLa cervical cancer cells [32]. Wheat germ extract (Avemar) has been reported to be involved in the apoptosis of MCF-7 breast cancer, Jukrat acute lymphoid leukemia T cell, HL-60 promyelocytic leukemia, H9 human lymphoid cell, and gastric cancer cells [33,34]. Avemar also was able to reduce nucleic acid synthesis in the tumor cell by altering the glucose uptake of cancer cells [33].

Whole grains also contain a significant amount of anti-nutrients (not all anti-nutrients are harmful to health), one such is a protease inhibitor. Protease inhibitors were shown to have inhibitory actions against cancer by the suppression of expression of neoplasia in cells (cells are already exposed to cancer) and by inhibiting the tumour promotion [22].

Inflammation

Inflammation is the outcome of the innate immune system triggered by obnoxious stimuli, microbial pathogen, and injury [35]. Continuous activation of the immune cells gives rises to the chronic inflammation. The initiation and progression of the cardio vascular disease, arthritis, diabetes, pulmonary disease, autoimmune diseases etc. accelerate chronic inflammation [36]. Chronic inflammation elevated levels of pro-inflammatory cytokines and acute phase proteins, such as interferons (IFNs), interleukin (Il)-1, Il-6, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) [36]. Ferulic acid has a high anti-oxidative activity and is also actively involved in the production of insoluble dietary fibre. The inhibitory activities of the ferulic acid against carcinogenic diseases has been attributed to the prevention of the formation of carcinogen compound from precursor compound and the blockage of the reaction of carcinogen with cellular macromolecules [22]. As stated previously, ferulic acid is present in relatively high quantities in wheat, indicated that wheat or its co-products could cause this mechanism. However, more studies are obviously needed to support this hypothesis

Other phytochemicals present in the whole grain play their own role to suppress carcinogenic or cardiovascular diseases, which leads to the chronic inflammation.

Cardiovascular Diseases

Lipid deposition, oxidative stress, vascular inflammation, smooth muscle cell differentiation, and endothelial dysfunction play a vital role in the formation and progression of the atherosclerotic plaque [36]. Nutrition interventions in the food habits have been associated with the lower risk of coronary heart diseases (CHD) [37]. Serum low-density lipoprotein (LDL) cholesterol (major risk factor for CHD) was reported to decrease with increased intake of soluble fibre, plant sterols and higher intake of whole wheat [38]. In another study, it was shown that phytoestrogen in isolation, but is also present in wheat, binds to a specific intracellular receptor, which in turn protects blood vessels from atherosclerosis [39]. This hormone promotes appropriate vasodilation of coronary arteries when increased blood supply is required. In yet another study, the phytoestrogen from whole wheat (enterolactone) was shown to have a protective effect on vascular events related to arterial spasm [40]. The consumption of 48-50 g of whole wheat (3-5 serving/d) was able to reduce the risk of CVD by 21% [41]. The total and LDL-cholesterol concentration were also significantly lower in their study.

Increased LDL cholesterol levels, hypertension, diabetes, obesity, sedentary life style, low antioxidant vitamin status, and hyperhomocysteniemia are some of the major risk factors for CHD [42]. Several studies on whole wheat have demonstrated the potential of whole wheat to alter these risk factors [40]. Whole wheat phytochemicals, beta-sitosterol (lowers cholesterol), dietary fibres, resistant starch, anti-nutrients, such as phytic acids, and tannin have been shown to lower plasma cholesterol and triglycerides [43].

Immunology

The immune system is a complex web of cellular interactions, which is influenced by health, genetics, and consumption of the foods [44]. Whole wheat contains a plethora of bioactive components, the consumption of which influences biochemical reactions in our body. Ferulic acid, the major bioactive component in whole wheat, contributes the functional immunity mostly by improving gamma delta T (γδ T) cell proliferation and function in the body [29]. γδ T cells are important immune cells that have the properties of innate and acquired immune systems [45]. Ferulic acid acted as a pathogen-associated molecular pattern (PAMP) for the γδ T cells [29]. The γδ T cells lysed cells via perforin of Fas-ligand-dependent pathways. These cells also secreted cytokines and chemokines in order to recruit monocytes and neutrophils to the site of inflammation. γδ T cells either recognize PAMPs, phosphor antigens or non-peptide, lipid antigens, and respond directly to Toll-like receptor (TLR) ligands without the presence of antigen presenting cells. In a recent study in mice, ferulic acid modulated the function of dendritic cells (antigen presenting cells) to promote interferon (IFN)-gamma production by activated T cells. Further it was explained that ferulic acids affected the Th2 based immune response. In addition, ferulic acid was determined to act as an antiallergic in treating Th2 mediated allergenic response [46].

Studies using dietary fibres present in whole wheat were able to stimulate the immune function via production of short-chain fatty acids (SCFAs) [47]. The addition of SCFAs to parenteral feeding has shown to increase T helper cells, macrophages, neutrophils, and cytotoxic activity of natural killer cells in animal studies [48]. Celiac disease (caused due to dietary intolerance of wheat), a chronic inflammation of the bowel, results from an autoimmune response due to the binding of gluten peptides to T cells of the immune system (only to those people who are allergic to wheat) with the human leucocyte antigens (HLA) DQ2 and DQ8 [7]. These bound peptides are recognized by specific CD^{4+} T cells and then releases inflammatory cytokinesis, which flattens the intestinal epithelium [7].

Gastrointestinal Microbiota

Arabinoxylan and cellulose (important components in whole wheat) are poorly fermented in the gut [49] and have high potential to improve/maintain a healthy gut. Consumption of whole grain was shown to increase bifidogenic effect: some strains of Bifidobacterium are markers of healthy gut [15]. An increase in butyrate-producing bacteria, Roseburia, Eubacterium rectale and the *Clostridium leptum*, contributed to host colonic epithelial cell energy during the fermentation of carbohydrates from the whole wheat [50]. A study has shown that dietary fibers provided significant health benefits by increasing viscosity, which delays gastric emptying and limits glucose diffusion towards the enterocytes for absorption [15]. Dietary fibre intake has also been associated with an increase in satiety thus help to control body weight [51]. The mechanism for this may be due to the hormonal effects mediated by the reduction of insulin secretion, the metabolic effect mediated by increased fat oxidation and colonic effects via SCFA production [22]. Decreases in the diversity of the microbiota are associated with increased risk of obesity and disease [43]. Whole wheat consumption increased the microbiota. Another compound, lignan in whole wheat was able to protect against hormonally mediated diseases [22]. Plants lignans are converted by gut bacteria to the mammalian lignans enterolactone and enterodiol. Saturated fat exhibits an antimicrobial effect and consequently reduced diversity [49]. Considering that whole wheat is lower in the total fat content but high in high unsaturated fat, these fats have been shown to produce a healthy microbial effect [48]. An increase in the Bifidobacteria and decrease in Coriobacteriaceae resulted when whole wheat was incorporated in diet. Bifidobacteria was correlated with plasma HDL-concentration, while Coriobacteriaceae was correlated with non-HDL cholesterol [48].

Metabolic Syndrome

Metabolic syndrome is a pattern of metabolic disturbances associated with increased risk of type 2 diabetes, raised blood pressure, dyslipidaemia, and obesity [52]. Several studies on intake of whole grains have been reported that consumption of wheat was negatively associated with metabolic syndrome [35,53]. Whole wheat flour has been able to improve glycaemic control and insulin sensitivity, decrease blood pressure and produce a healthy body mass index (BMI) as discussed in reference [22]. The mechanism for the above response was due to the presence of bran, which decreased glucose absorption and produced SCFA from the fermentation of resistant carbohydrates, which in turn improved insulin sensitivity [53].

Yet another study, tocotrienols in whole wheat decreased the risk of heart disease whereas β-sito sterol was associated with a decrease in cholesterol [34]. A study with ferulic acid, which is the major component in whole wheat, showed that ferulic acid converted into DHFA by microbiota in gut resulting an increase in Bacteroidetes and Firmicutes [54]. γ–oryzanol (γ–oryzanol content in wheat bran ranged from 300-390 mg/kg) observed in wheat barn showed to lower serum cholesterol effectively than tocopherols and tocotrienols [55]. Low-density cholesterol (LDL) was shown to be reduced by 12% and ratio of LDL to HDL (high-density lipoprotein) cholesterol was decreased by 19% when diets containing γ–oryzanol were fed to rats (Mitchell et al., 1996). That arabinoxylan reduced the postprandial glucose level due to its high viscosity [56]. As a result, arabinoxylan reduced small intestinal motility resulting in delayed glucose absorption; hence a flat postprandial glucose response was observed.

Whole Wheat Prospects and Lacks

The diversity of the nutraceuticals present in whole wheat makes this bran an excellent commodity on our diet plates. Several studies have been carried out over a decade, to identify its multiple health benefits including cellular oxidation mediated diseases, cancer, atherosclerosis, inflammation, obesity, and diabetes [5,22] as described throughout this documents. The presence of polyphenols in whole wheat was correlated with the reduced risk of the diseases. However, most of the studies were focused either on the individual action of the polyphenols, supplementation of the wheat/wheat extract *in vitro*. Only very few studies reported the effect on health due to the overabundance of specific phytochemicals. Will the effect be beneficial or detrimental? Also, the bioavailability of the proposed phytochemicals in presence of anti-nutritional factors is another crucial concern. Several studies have reported the binding of polyphenols with trypsin inhibitors during digestion [57]. The fact that humans may have other diseases and allergic response, the beneficial effects of polyphenols on these groups of people is not yet known. Will the unhealthy people have a similar effect or a new health complication may take place? Moreover, the analytical method used can vary the amount of polyphenols [58]. A unique and consistent approach to quantify compounds may give a reliable results considering their chemical diversity and their interactions with a given food matrix. Besides above-mentioned questions, a number of phytochemicals in wheat are largely depended on the growing conditions of wheat and therefore, probably each food type will have to be optimized on its own merit.

Given the fact that polyphenols are produced in plants to protect them against stresses (biotic and abiotic), how relevant it is in terms of total production of wheat. There lacks the specification in the classes of wheat that were being used in the study. Compared to white wheat, red wheat contains higher levels of polyphenols, but what about the bioavailability of those compounds. An abundance of polyphenols does not really assure higher bioavailability. Studies on diverse group of the population also may help to pronounce effect of phytochemicals on wheat. In presence of stresses, the total production decreases, but polyphenols may increase in those grains. Will the phytochemicals derived from unhealthy grains be useful to us?

In the recent years, besides health benefits from whole wheat several studies have shown the negative or possible problems due to the consumption of whole grains. Given the possibility of contamination of heavy metals on whole wheat and their possible adverse effects on human health, it is important to study if whole wheat is actually beneficial or not. Also, the contamination of whole wheat by nanoparticles such as zinc oxide and titanium dioxide [59,60] and their potential effects to health has been a major concern regarding the use of whole wheat in our diet. The ability of nanoparticles to cross the blood-brain barrier, move to other vital organs, and possible damage of DNA [61] makes whole wheat questionable in its potential benefits. The contamination of nanoparticles from the different sources in an environment to plant and finally to grains [59] is the serious issue and more studies need to be carried out. The amount of heavy metals that reaches on our diet plate, their potential to exacerbate other benefits either by binding with phenols or by acting as inhibitory agent: these all areas need to be addressed.

Concluding Remarks

Although presence of anti-nutrients and binding of phenolic acids with protein may have adverse effect on health, whole wheat and whole wheat based products played a great role to improve health by preventing major diseases and disease conditions. However, thorough study on the types of wheat, interaction of the phytochemicals with other proteins, heavy metal accumulation in wheat bran, bioavailability of compounds in different wheat products need to be addressed in future, which will give us a big picture of the beneficial effects of one of the largely consumed products in world.

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