Wheat Nutraceutomics: Breeding, Genomics, Biotechnology, and Nanotechnology

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Abstract

Wheat is humanity's second most important cereal crop, consumed widely in developed and developing countries and constituting a major source of protein and energy, especially in the developing world. Wheat grain, including the bran and endosperm, furnishes diverse macro-and micronutrients required for the normal physiological and biochemical functioning of the human body. Dietary deficiencies of micronutrients such as iron (Fe) and zinc (Zn) lead to severe health consequences in children below 5 years of age and in pregnant women and lactating mothers. Increasing the nutritional value of wheat grain can largely address micronutrient malnutrition for the world's growing population. The recent availability of wheat genome sequence library in the public domain, together with the expanding horizon of next-generation sequencing, and genome editing technologies, holds great promise for trait-based molecular breeding to develop nutrient-rich wheat cultivars. Modern biofortification techniques, including conventional breeding, transgenics, and agronomic biofortification, have already increased wheat grain nutrient content and the nutrient-rich biofortified wheat cultivars grown over 2 million ha area in South Asia & Latim America. This chapter discusses the importance of wheat in the human diet, wheat grain's nutritional composition, and advances in molecular and transgenic and genome editing approaches to develop health-related traits in wheat grain.

Keywords

Micronutrients · Malnutrition · Genome editing · Genomic selection · QTLs · Genetic engineering

1 Introduction

1.1 The Importance of Wheat

Wheat, an annual herb belonging to the family Gramineae or Poaceae, is a food crop grown and consumed in nearly 100 countries and imported and consumed in many others where western-style diets are being adopted (Cummins and Roberts-Thomson 2009; Shewry 2009). Common hexaploid wheat (*Triticum aestivum* L., $2n = 6x = 42$, AABBDD) is one of the most important staple crops in the world, serving as a key food source for 30% of the human population and contributing approximately 20% of its energy needs (calories) and 25% of its dietary protein (Borisjuk et al. 2019). Its grain is used in bread, supporting the baking industry, and popular foods such as chapatis, noodles, and cookies, to name just a few. Worldwide wheat cultivation ranges from 67° N in Scandinavia and Russia to 45° S in Argentina, including elevated regions in the tropics and sub-tropics (Feldman 1995; Shewry 2009). About 95% of wheat grown worldwide is hexaploid bread wheat (*Triticum aestivum* L.), with most of the rest being tetraploid durum wheat (*T. turgidum* var. *durum*), which is adapted to dry, Mediterranean climates and used in pasta. Minor amounts of primitive wheats are also grown mainly for specialty health foods, including einkorn (diploid *Triticum monococcum*), emmer (tetraploid *T. turgidum* var. *dicoccon*), and spelt (hexaploid *T. aestivum* var. *spelta*) in certain areas of Spain, Turkey, the Balkans, and the Indian subcontinent. The latter differs from bread wheat essentially in that the hull is not removed by threshing, resulting in a higher fiber content when consumed as whole grain (Brouns et al. 2013).

Cultivation of wheat started about 10,000 years ago as part of the Neolithic Revolution, when humans switched from hunting and gathering to settled agriculture. The earliest cultivated forms were diploid (einkorn with genome AA) and tetraploid (emmer with genome AABB) wheats from southeastern Turkey (Brouns et al. 2013; Dubcovsky and Dvorak 2007). Hexaploid bread wheat (AABBDD) is believed to have emerged some 9000 years ago through spontaneous hybridization between a cultivated tetraploid (*Triticum turgidum;* AABB) and goat grass (*Aegilops tauschii;* DD) (Brouns et al. 2013; Feldman 2001). The earliest cultivated forms were landraces presumably selected from wild populations by ancient farmers, considering their superior yield and other agronomical important characteristics, a domestication that separated modern wheat genetically and phenotypically from its wild relatives and early forms.

Wheat grain production amounted to over 780 million tons (t) harvested from more than 225 million hectares (ha) in 2019–2020 (http://www.fao.org/faostat); but wheat is still the third major food crop, lagging behind maize and rice both in yield and the application of genomic tools for crop improvement (Borisjuk et al. 2019; Uauy 2017). Average wheat yield worldwide increased nearly three-fold during the Green Revolution of the mid-to-late twentieth century, largely due to expanded irrigation, intensive fertilizer application, and advanced breeding methods (Evenson and Golin 2003a), but the current global average yield around 3 t/ha is far below the crop's genetic potential (Langridge 2013), aside from yield gaps relating to crop management. As estimated by Langridge (2013) and Henry et al. (2016), to meet the wheat consumption demands (expected to rise 1.6% annually) of an estimated 9.5 billion world population by 2050, wheat yields should grow by over 60% to approximately 5 t/ha, coupled with maintaining or improving its nutritional characteristics and using currently available land. Facing this challenging scenario, which includes rising temperatures and alarming water scarcities, the emphasis must be on improved productivity and adapting to environmental challenges (Borisjuk et al. 2019).

1.2 Wheat's Importance in Times of Chronic Disease and Malnutrition

Malnutrition can be classified as under-nutrition (hunger, micronutrient malnutrition/hidden hunger) and over-nutrition (overweight/obesity). For malnourished children under 5 years of age, 149 million are stunted, 49.5 million are wasted, and 40 million are overweight (Development Initiatives 2020; Poole et al. 2021). About 45% of mortality among children aged five and below is associated with malnutrition, chiefly in low- and middle-income countries. In the early 2000s, more than 3 billion people were micronutrient malnourished (Šramková et al. 2009). More recently, some 528 million (29%) women of reproductive age are anemic from a lack of dietary iron, making iron deficiency the most widespread micronutrient deficiency in the world (Choge 2020). Dietary deficiencies of zinc, a critical micronutrient, are widespread, accounting for malnutrition-related developmental impediments across all age groups. Lethal effects amount to 800,000 child deaths annually, with vulnerability concentrated in sub-Saharan Africa and South Asia. Staple cereals such as wheat are significant sources of both minerals, contributing 44% of the daily intake of iron (15% in bread) and 25% of the daily intake of zinc (11% in bread) in the UK (Henderson et al. 2007; Shewry 2009). According to an estimate, almost 690 million people suffered from hunger in 2019, worsened by the worldwide COVID-19 health pandemic. The number of hungry people is expected to exceed 840 million by 2030 – almost 10% of the global population (Poole et al. 2021). While humankind is fighting malnutrition on one front, over-nutrition is increasing globally: nearly half of the world's adult population is overweight or obese, and three-quarters of those persons live in low- and middle-income countries (Poole et al. 2021). Worldwide incidences of diabetes (44%), ischemic heart disease (23%), and certain cancers (7–41%) are linked to being overweight and obese.

Child stunting often results from micronutrient malnutrition tied to imbalanced diets in children and mothers, especially among the poor. Food-based approaches to prevent malnutrition and which focus on micronutrients can help address "hidden hunger." Cereal-based allergies and intolerance have also posed serious concerns. Major chronic diseases include obesity, heart ailments, cancer, and celiac disease, among others, taking a heavy toll on health and the world economy. In the current context of chronic diseases, wheat, its bioactives, and products assume relevance and need to be deliberated in a multifarious context.

1.3 The Limitations of Conventional Breeding and Rational for Next-Generation Breeding: Nutritional Perspectives

Wheat underwent hybridization and genome duplication to generate its hexaploid genome (2n = 6x = 42, AABBDD). Bread wheat possesses a sesquipedalian genome – 17 gigabases – which is over 5 times larger than the human genome and 40 times the size of the rice genome. Recent estimates document 107,891 high-confidence genes in bread wheat, with over 85% repetitive DNA sequences, representing a three-fold redundancy associated with being hexaploid. Every year, conventional commercial breeding produces a large number of new crop varieties to improve productivity and nutrition, strengthen food security, and increase consumer acceptability (Govindan et al. 2022). The conventional breeding process has evolved to provide an effective framework for improving crop performance while also assisting in the development of safe and nutritious foods. Conventional plant breeding entails identifying desirable parents in order to create favorable combinations in the next generation (Kaiser et al. 2020). This selection of a few individuals from a large population is an important component of the plant breeding process (Kaiser et al. 2020). Conventional breeding has made significant contributions to large-scale cultivation, yield potential, and the frequency of desirable traits in wheat; however, it has certain boundaries that should be considered under current conditions, and a new wheat breeding strategy is required (Borisjuk et al. 2019).

Wheat's hexaploid genome and associated functional gene redundancy make genetic advances to selecting a desired phenotype difficult, if not impossible, due to gene linkage or gene drag. Further advancement in wheat breeding is dependent on understanding of functional genomics. Grain yield and quality can be improved by identifying the most important key genes, as well as their structures, roles, and functions in wheat plant development. This functional genomics knowledge can then be used to change the structures and functions of selected key genes via genetic manipulation (Borisjuk et al. 2019), a broad term used here to describe molecular methods whose products fall outside the traditional definition of "genetically modified" (GM) such as RNA interference (RNAi) and clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein (CRISPR/Cas9) Borisjuk et al. 2019). Such approaches will be critical in determining the functions of wheat genes. By using cutting-edge technology like genome sequencing and targeted mutations using genome editing methods like CRSPR-Cas and RNAi, it is possible to increase the resilience of wheat while reducing environmental pollution (Gupta and Karkute 2021). However, the use of CRISPR/Cas systems depends on knowledge of the targeted gene's sequence. Through homology directed repair (HDR), precise substitution of an existing allele has substantially benefited crop improvement with elite alleles in commercial types. Base editing, prime editing (PE), genome sequencing, genome-wide association study (GWAS), speed breeding, high-throughput genotype and phenotype profiling, and synthetic biology are a few examples of contemporary methods (Gupta et al. 2022). The ability to accurately replace one base with another by base editing, an alternative and powerful method for HDR-mediated gene replacement, has made it possible to accurately replace an allele with a single nucleotide polymorphism (SNP) (Komor et al. 2016). Many base substitutions (12 types) and minor insertions-deletions (indels) are made possible by prime editing (PE), which increases the reach and potential of precision genome editing. Recent studies have shown that RNAi, a frequent mechanism for controlling gene expression in eukaryotic cells, is a reliable tool for functional genomics and the engineering of novel phenotypes. The method relies on the expression of small interfering RNA (siRNA) molecules, such as antisense or hairpin RNAi constructs, to affect post transcriptional gene silencing in a sequence-specific manner (Borisjuk et al. 2019). RNAi applications in wheat.

2 Detailed Nutritional Composition of the Wheat Grain

Grain is the harvested and economically important part of the wheat plant, and its biochemical composition determines its nutritional and health properties (Shewry 2009). Table 1 details the generalized composition of various chemical constituents. On a dry weight basis, a wheat grain can be divided into three distinct parts: mealy

Table 1 Contents and variations in chemical composition of wheat grains (dry weight)

Parameter	Range (%)	References
Carbohydrates (%)	85	Stone and Morell (2009)
Starch (20–30% amylose and 70–80% amylopectin)	55–75	Borisjuk et al. (2019)
Dietary fiber/non-starch/cell wall polysaccharides (%)	11.5–15.5	Andersson et al. (2013)
Fats (%)	2.0–2.5	Gonzalez-Thuillier et al. (2015)

endosperm (80–85%), outer bran (13–17%), and germ (2–3%). (Belderok et al. 2000). The endosperm occupies the majority of the wheat grain, primarily consisting of starch and proteins with small amounts (2%) of fiber. The endosperm provides energy to the seed, making available carbohydrates and proteins during germination. The germ, the smallest segment of grain, contains lipids, sterols, antioxidants, vitamins (B, E), minerals, and enzymes, as well as nourishing the seed. The bran is a seed's outer shell that contains fiber, vitamins, and trace minerals. The outer pericarp (3–5%) contains insoluble dietary fibers and bound phenolic acids (which act as antioxidants), whereas the aleurone layer (6–9%) contains dietary fibers, proteins, enzymes, phenolic compounds, vitamins (B-complex), minerals, and phytates. The testa (1% of the total) contains trace amounts of alkylresorcinols, sterols, and steryl ferulates. Wheat bran may typically contain dietary fiber (42.8%), other carbohydrates (21.7%), protein (15.6%), ash (5.8%), and lipids (4.3%).

There is a need for suitable and efficient methods to test diverse wheat genotypes for various quality parameters, as documented in the updated listing by Gupta et al. (2022). Model-based methodologies are being developed to identify superior wheat lines in early generations of breeding cycles (Mohan et al. 2022).

2.1 Carbohydrates

Carbohydrates account for the majority of wheat grain (up to 85%) (Stone and Morell 2009). Starch accounts for the majority of stored carbohydrates, accounting for 55–75% of grain dry weight (Borisjuk et al. 2019). Fibers and low-molecular-mass mono-, di-, and oligo-fructans are examples of others (Table 1). Wheat grain starch is found in either large lenticular granules of 25–40 m, which develop during the first 15 days after pollination, or small spherical granules of 5–10 m, which develop 10–30 days after pollination and account for approximately 88% of total grain starch granules (Belderok et al. 2000). Starch is a polymeric form of glucose that is chemically classified as amylose and amylopectin. Amylose has a molecular weight of around 250,000 and may contain nearly 1500 glucose units with wide variations. Amylose is thought to have a linear polymer structure, with -(1,4)-glycosidic linking glucose moieties together and a degree of polymerization (DP) of 1000–5000 glucose units. The structure of this polymer was previously assumed to be primarily linear, but this appears to be true for only a portion of the amylose; the remainder is slightly branched. The branching in amylopectin is to a much greater extent than in amylose and the average unit chain of amylopectin has only 20–25 glucose molecules, with an average molecular weight of about 10^8. Amylopectin is a much larger polymer with a DP ranging from 105 to 106 glucose units tethered via α-(1,4)-linked glucose polymers, which are further connected by α-(1,6)-linkages (5–6%).

2.2 Dietary Fiber

Dietary fiber is defined as lignin plus plant polysaccharide components that are indigestible by human digestive enzymes. While soluble fiber (pectic substances, hydrocolloids, -glucans) is water soluble, insoluble fiber (cellulose, hemicellulose, lignin, arabinixylans) is not. Regular consumption of dietary fiber, which is primarily found in whole grains, protects against heart disease, hypertension, hyperlipidemia, type 2 diabetes, obesity, constipation prevention, diverticular disease, esophageal disease, and a variety of cancers (Poole et al. 2021; Weickert and Pfeiffer 2008). Soluble fiber such as β-glucan [(1→3,1→4)-β-D-glucan] effects glycemic index and appears to help prevent chronic diseases like diabetes and obesity and, possibly, negative effects associated with FODMAPS (fermentable oligo-, di-, monosaccharides and polyols) (Poole et al. 2021). Arabinoxylans (AX) and (1→3),(1→4)-β-glucans are housed primarily in wheat endosperm cell walls. Arabinoxylans yield short-chain fatty acids, particularly butyrate, in the colon. It is conjectured that high butyrate concentrations in the colon improves bowel health and lower cancer risk.

2.3 Proteins

Proteins are required for various body functions, ranging from enzymatic, structural to locomotory and many more. Protein content in wheat grain ranges from 10 to 15% (dry wt.) (Borisjuk et al. 2019). Wheat proteins are classified according to their extractability and solubility as per Osborne and have been highlighted in Table 2 In general, cereal proteins are low in the essential amino acids lysine (1.5–4.5% vs. 5.5% of WHO recommendation), tryptophan (Trp, 0.8–2.0% vs. 1.0%), and threonine (Thr, 2.7–3.9% vs. 4.0%).

2.4 Lipids

Lipids are present in small amounts (2–2.5%) in wheat but have a significant impact on food quality and texture because they can bind to proteins and starch to form inclusion complexes. The germ contains nearly 11% of total lipids, but significant amounts are also associated with the endosperm's bran, starch, and proteins

Table 2 Types of wheat proteins with their solubility and other features

Protein name	Solubility	% of Total protein	Features
Albumins	Water soluble	Smallest in size (10%)	Most of physiologically active enzymes belong to these two; both proteins are present in the seed coat, the aleurone cells and the germ, with a lower concentration in the mealy endosperm; both make up 20–25% of total wheat proteins
Globulins	Insoluble in pure water; soluble in dilute NaCl solutions, but insoluble at high NaCl concentrations	Size more than albumins (10%)	
Gliadins	Soluble in 70% ethyl alcohol	Size more than above two (45%)	High-molecular-weight storage proteins for future use by the seedling located in the mealy endosperm; both constitute 75–80% of total wheat proteins; both are unique, being biologically active: though they have no enzyme activity, they function in dough formation through gas retention, producing spongy baked products
Glutenins	Soluble in dilute acid or sodium hydroxide solutions	Low- and high-molecular-weight types (35%)	

Source: Belderok et al. (2000), Borisjuk et al. (2019), Šramková et al. (2009)

(Poole et al. 2021). All fractions contain significant amounts of free fatty acids and triacylglycerols (Gonzalez-Thuillier et al. 2015). Phosphatidyl choline, phosphatidyl ethanolamine, and phosphatidyl serin are the most common bound lipids, followed by lysophosphatidyl derivates with one free hydroxyl group on the glycerol moiety. The main sterols were identified as -sitosterol, campesterol, and saturated sterols C28 and C29. Numerous studies have shown a high level of linoleate (C18:2) in both the total lipid and the triglycerides.

2.5 Vitamins

Over 3 billion people are currently micronutrient malnourished, which means their diets are deficient in micronutrients such as vitamins. Vitamins are a diverse group of food-based, essential, small organic substances that are synthesized by plants and microorganisms rather than the human body. They do not provide energy but are essential micronutrients for humans, acting as coenzymes or their precursors (niacin, thiamin, biotin, pantothenic acid, vitamin B6, vitamin B12, and folate) or in specialized functions such as vitamin A in vision and ascorbate in specific hydroxylation reactions. Vitamins play roles in human genetic regulation and genomic stability (folic acid, vitamin B12, vitamin B6, niacin, vitamin C, vitamin E, and vitamin D) as well as antioxidative defense systems (vitamins C and E and some carotenoids) (Poole et al. 2021). The vitamins in wheat and their range are presented in Table 3.

Table 3 Vitamins, phenolics, minerals, and anti-nutritional factors composition in wheat grains

Major component	Name	Range	References
Vitamins	Vitamin B1 (Thiamine) (mg/kg)	5.53–13.55	Shewry et al. (2011)
	Vitamin B2 (Riboflavin) (mg/kg)	0.77–1.40	
	Vitamin B3 (Niacin) (mg/kg)	0.16–1.74	
	Vitamin B5 (Pantothenic acid) (mg/kg)	0.88–4.04 (Durum)	Tekin et al. (2018)
	Vitamin B6 (Pyridoxine) (mg/kg)	1.44–3.05	Batifoulier et al. (2006)
	Vitamin B9 (Folates) (mg/kg)	0.323–0.774	Piironen et al. (2008)
Minerals	Magnesium (mg/kg)	600–1400	Oury et al. (2006)
	Iron (mg/kg)	18–40	Ram and Govindan (2020)
	Zinc (mg/kg)	21–63	
	Copper (mg/kg)	1.8–6.2	
	Manganese (mg/kg)	24–37	
Phenolics	Phenolic acids (μg/g)	326–1171	
Anti-nutritional factors	Phytic acid (mg/g)	12–18	

2.6 Tocols

The germ fraction of t einkorn accessions and some bread wheat seed showed the highest concentrations of -tocopherol and total tocols. The bran fraction had the highest levels of -tocotrienol, but significant amounts were also found in the flour.

2.7 Minerals

Table 3 summarizes the minerals that are available in wheat, as well as their generalized availability ranges. The topic of two vital minerals, iron and zinc, has been addressed here. Plants primarily store iron in the form of ferritin structures, which accumulate primarily in non-green plastids, etioplasts, and amyloplasts (Borisjuk et al. 2019). Iron has been found primarily in the aleurone layer (bran) of wheat grains, where it has complexed with phytate (myo-inositolphosphate 1,2,3,4,5,6-hexa-kisphosphate). These complexes are insoluble, limiting iron bioavailability in humans and livestock. Scientists are experimenting through breeding to express phytase enzymes in developing grain and thus increase mineral availability. The discovery of a heat-stable form of this enzyme would allow phytate complex hydrolysis to occur during food processing. Another option is to increase the concentration of Fe in grains. In 1994, Fe concentrations in a wheat variety grown at the CIMMYT research station in El Batán, Mexico, ranged from 28.8 to 56.5 mg/kg (mean = 37.2 mg/kg). Peleg et al. (2008) reported new wild emmer wheat accessions with very high Fe (up to 88 mg/kg) and Zn (up to 139 mg/kg)

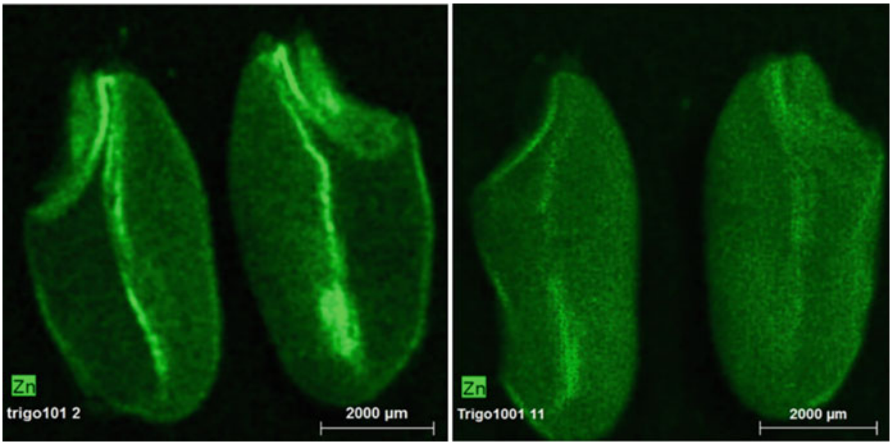

Fig. 1 Localization of zinc in wheat grain with µXRF (left high zinc wheat 'Zinc-shakti', right CIMMYT control variety 'Baj')

concentrations, as well as high protein content (up to 380 g/kg) and tolerance to drought and Zn-deficient soils.

Zn deficiency causes nearly 500,000 deaths in children under the age of five each year (Borisjuk et al. 2019). Micronutrient levels in modern elite wheat cultivars are typically suboptimal. Given the high concentrations of Zn and Fe in the outer husk, aleurone, and embryo, both micronutrients are lost during milling and polishing. Phytate, an anti-nutritional factor, reduces micronutrient availability in the human digestive tract. Zn deficiency affects nearly 33% of the world's population, resulting in health complications such as stunted physical development, weakened immunity, and decreased learning ability, among other things. According to a variety of reports and survey studies, the average Zn concentration in whole wheat grain is from 21 to 63 mg/kg (Ram and Govindan 2020). Most of wheat grain Zn is in the embryo and aleurone layer, with a small portion in the endosperm (Fig. 1).

3 Marker-Assisted Breeding for Health-Related Traits

Genetic tools can accelerate genetic gains for yield and stress resilience by assisting in precise and accurate selection, saving time, money, and labor in crop improvement. Breeding approaches combine modern cutting-edge genomic tools and breeding tools to accelerate breeding progress. Molecular marker-assisted selection (MAS), backcross breeding (MABB), and recurrent selection (MARS) aid in the early identification of favorable alleles for economically important traits (Bonnett et al. 2005). It should also be noted that the requirements for selecting markers, as well as overestimation of marker effects with minor contributions, can limit the effectiveness of using molecular markers in MAS. In wheat, MAS aids in the improvement of agriculturally important traits by allowing efficient screening of difficult-to-estimate traits, the transfer of genomic regions from genetic stocks rich in desirable traits into better backgrounds, and the pyramiding of different polygenic characters. The discovery of numerous QTL-specific molecular markers for monogenic and polygenic traits in recent years has accelerated the deployment of molecular markers for regions associated with biotic and abiotic resistance, as well as other economically important traits. The cost of more precise genotyping, high-throughput genotyping and phenotyping, and the use of imaging and computational traits have all reduced the cost of biotechnological tools.

3.1 Germplasm Characterization

The high level of variability in nutritional traits found in wild relatives and land races of wheat allows for the development of high-yielding nutrient-rich wheat varieties (Cakmak 2008). The traits required for desirable processing and end-use quality, as well as nutritional traits, are being transferred from wild relatives of wheat, such as *Aegilops tauschii*, *Triticum turgidum* ssp. *diccocoides*, *Triticum turgidum* ssp. *dicoccum*, and *Triticum aestivum* ssp. *spelta* species, to high-yielding bread wheat lines that feature high yield and better adaptation (Guzmán et al. 2014). *T. dicoccon*-based synthetic hexaploids, landraces from Iran, Spain, and Afghanistan, and *T. dicoccoides* from Israel and adjacent regions are being used to improve micronutrients. CIMMYT Mexico has a large collection of genetic resources in its germplasm bank near Mexico city.

Screening for micronutrient variability has demonstrated that landraces and wild relatives of common wheat such as *T. spelta* and *T. dicoccon* have the ample amount of Zn and Fe. Contemporary breeding methods employ limited backcrossing procedure to introgress high-Zn/Fe genes from *T. spelta,* synthetic hexaploids, and landraces into better agronomy genotypes available with the breeders.

Ae. peregrina accessions have more than double grain Fe and Zn concentrations than elite wheat cultivars. Some of the derivatives of fertile wheat x *Ae. peregrina* with bolder seeds, better harvest indexes comparable to those of elite wheat lines, and higher micronutrient concentrations demonstrated that *Ae. peregrina* possesses a separate genetic system for biofortification, similar to that of *Ae. kotschyi*. The fertile BC_2F_2 plants with one or more additional chromosomes from *Ae. peregrina* showed a 100–200% enhancement of grain Fe and Zn levels over those of normal, elite wheat lines. Further analysis showed that the two chromosome groups 7 and 4 of *Ae. peregrina* had genomic regions for micronutrient content in wheat.

3.2 Marker-Assisted Gene Introgression

The use of MAS can make conventional wheat breeding programs more cost-effective and time-efficient (Gupta et al. 2010). It has primarily been used in wheat for foreground for carrier chromosome or segment selection and background selection for maximum genome recovery. It has recently been used successfully to

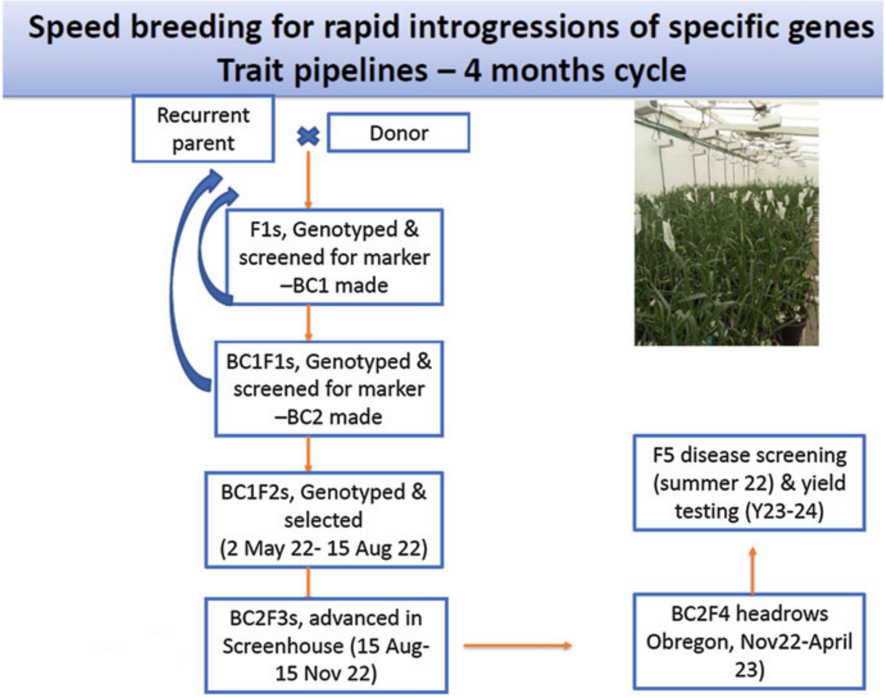

Fig. 2 Trait augmentation program at CIMMYT, Mexico

introduce and pyramid major genes/QTL for desirable wheat characteristics of a major locus (Gpc-B1) on chromosome 6BS that was introgressed from wild emmer wheat (*Triticum turgidum* ssp. *dicoccoides*) has improved Fe (18%), Zn (12%), and protein (38%). A marker called *Xuhw89*, which is closely related to the (0.1 cM) *Gpc-B1* locus (Distelfeld et al. 2006), has aided in the development of wheat varieties with high Fe, Zn, and protein concentrations. Many RFLP, SSR, and CAPS markers have been linked to this marker *Xuhw89* (Distelfeld et al. 2004). With the cloning and characterization of *Gpc B1* locus, a gene-specific marker and the locus has been introduced in wheat, improving GPC without a yield penalty (Kade et al. 2005). This has occurred mostly in many wheat growing regionssuch as India where it has transferred to elite cultivars. The wheat breeding program at CIMMYT recently embarked upon to introgress key agronomic, disease resistance and nutritional quality traits through its speed breeding pipeline (Fig. 2).

3.3 Gene Pyramiding

Functional markers are critical for gene stacking, genomic region transfer, and gene editing procedures. So far, 97 functional markers in bread wheat have been used to establish 30 loci from 93 alleles (Alotaibi et al. 2021). With the advancement of genomic studies, the number of alleles has increased, and approximately 157 markers for 100 loci for various traits of economic importance have been identified. Few genes, including *VRN1* and *Gpc-B1*, have been successfully incorporated using the conventional positional cloning approach in wheat. Similarly, genes related to grains, such as *TaGS5*, *TaGS3*, and *TaCwi-A1* related to grain size; the *Psy1* (He et al. 2009) phytoene synthase gene and *Zds1* related to zeta-carotene desaturase have been reported using competitive genomics methods.

4 Identification, Cloning, and Characterization of Health-Related Genes/QTLs

Micronutrient effectiveness has a complex nature that is influenced by the environment. It is critical for MAS and map-based cloning to identify the genes/QTLs that influence micronutrient content. Map-based cloning is a method for cloning the gene of interest without prior knowledge of its product. The basic requirement for map-based cloning is a population that has been systematically developed for the desired trait and is suitable for fine mapping. Precision genotyping and phenotyping for the trait aid in the generation of an accurate genetic map indicating the location of the gene. To determine the physical location, two nearby markers are used to screen BAC libraries. The candidate genes are discovered through chromosome walking and target interval sequencing. Significant progress has been made since cloning of the first gene. The gene *Gpc-B1* has been positionally cloned in wheat; it is 7.4 kb (md) long and encodes for NAC transcription factors controlling senescence, protein content, and Zn and Fe content.

A major QTL (18.3% phenotypic variation) in rice for Fe content on chromosome 8 of rice and shows synteny with chromosome 7 of wheat. Similarly, in a *T. durum x T. dicoccoides* cross combination, Peleg et al. (2008) discovered a major locus Fe content on chromosome 4 and two co-located loci on chromosome 7 for both Fe and Zn. Discovered major QTL on chromosome 7A for both micronutrients in a *T. boeoticum* and *T. monococcum* population. Xu et al. (2012) discovered 9 additive and 4 epistatic QTL on the 4B and 5A chromosomes, indicating a shared inherent basis for the three nutritional traits. Populations of diploid wheats, durum wheats, and wild Emmer wheat (Peleg et al. 2009), as well as synthetic wheats and *T. spelta*, were used to map QTLs for grain Zn and Fe concentration. In a separate report, Srinivasa et al. (2014) identified 10 QTLs (five each for Zn and Fe accumulation) that were widely distributed across 7 chromosomes. In a DH (doubled haloid) population, two QTLs for Zn content were found on chromosomes 1B and 2B. In addition, four genes governing the inheritance of grain Zn content were discovered in two mapping populations derived from a *T. spelta* x bread wheat combination (Srinivasa et al. 2014). Identified several QTLs on chromosome 7B accounting for 32.7% of total phenotypic variation for Zn concentration and a single QTL location on 4A accounting for 21.14% of total phenotypic variation for grain Fe content in two RIL populations derived from *T. spelta* L. and synthetic hexaploid wheat crosses. The majority of studies have found a statistically significant positive relationship between grain Zn and Fe concentrations in various environments where QTLs or similar genetic effects have regulated the Fe and Zn content in wheat. Co-localization of Fe and Zn concentrations has also been shown on chromosomes 2A, 2B, 4BS, and 5A (Xu et al. 2012) and 6B. This co-location of QTLs offers an opportunity to pursue a single marker-assisted program to enhance the concentrations of both Zn and Fe content. Table 4 provides a comprehensive list of major genes/QTLs identified in wheat for various quality traits.

5 Genomics-Aided Breeding for Heath-Related Traits

In wheat, genome-wide association studies (GWAS) have been widely used to investigate the genetics of quantitative traits. In comparison to traditional QTL mapping, GWAS provides better QTL resolution and wider allelic coverage, and it can be used on a larger population of genetic resources, landraces, varieties, or advance lines. Only a few studies in wheat have been conducted to better understand the genetic mechanism of quality characters. Nonetheless, improved genotyping facilities and access to the wheat genome reference sequence, RefSeq v.1.0, can speed up the identification and prediction of markers and their effects on trait. It would improve trait mapping, gene discovery. Detection of SNP markers that are distributed genome wide offers new avenues for genetic improvement of bread wheat for yield and traits of economic importance (Juliana et al. 2019).

GWAS and interval mapping studies in wheat have resulted in the identification of hundreds of markers for improving Fe and Zn concentration, but only a few have been used in marker-assisted breeding for nutritional traits. The only example is the *Gpc-B1* gene, which has been used to improve Fe, Zn, and Protein concentration in wheat using a MAS approach. Developed chromosome substitution lines in the variety ‘Langdon’ (LDN) and reported that a locus *QGpc.ndsu-6B* with a phenotypic variation of 66% is located on the 6B chromosome and contributes to high GPC. The wild allele at the locus accelerates leaf senescence and reduces grain size, resulting in yield reduction. *Gpc-B1* regulates senescence and nutrient remobilization, according to studies. Normally, wheat cultivars carry a non-functional *NAM-B1* allele, which is produced by a frame shift mutation in the wild allele, and this non-functional allele was preferred during wheat domestication. The presence of this allele on chromosome 6BS in wheat (Brevis and Dubcovsky 2010) allows for more time for grain development, which increases grain size and yield. In a study of 367 global bread wheat genotypes, only 5 Fennoscandian cultivars were found to have functional *Gpc-B1* or *NAM-B1* alleles, and these genotypes were only present for a short time in northern Europe. According to the wild-type/functional *Gpc-B1* allele has been conserved during the process of domestication. The MAS to transfer the wild-type *Gpc-B1* gene from Canadian to Australian varieties and found no yield penalty. Reported function loss caused by GPC1 and GPC2 mutations. GPC was found to be negatively associated with grain yield and influenced by genetic background in the majority of studies (Brevis and Dubcovsky 2010), and it is positively correlated with protein, iron, and zinc content with slight negative effect on yield. It is also suggested

Table 4 QTLs for Fe, Zn, and Selenium content in the grain of wheat and wild species

S. No	Cross/parents	Traits	QTLs	References
1.	*Triticum dicoccoides*	Fe & Zn	*GPC-B1* (6 7 BS)	
2.	*Triticum dicoccoides*	Fe & Zn	*TtNAM-B1*	
3.	*Hexaploid wheat (6x)* W7984 × Opata85			
4.	Hanxuan l0 × Lumai 14			
5.	RAC875-2 × Cascades			
6.	RIL (*Triticum boeoticum* × *Triticum monococcum*)	Fe	*QFe.pau-7A, QFe.pau-2A*	
7.	*Tetraploid wheat (4x)* Langdon × Accession #G18-16			Peleg et al. (2009)
8.	RIL (Xiaoyan × 54 Jing 411)	Fe & Zn	*QZn-5A, QFe-5A2, QGpc-5A1, QGpc-6A*	Xu et al. (2012)
9.	Tabassi × Taifun			
10.	*Tetraploid wheat (4x)* LDN × G18-16	Se		
11.	Berkut 9 × Krichauff			
12.	SHW L1 × Chuanmai32 & Chuanmai32 × Chuannong16	Fe, Zn & Se		Pu et al. (2014)
13.	RIL (PBW343 × Kenya Swara)	Zn	*QGzncpk.cimmyt-1BS,* *QGzncpk.cimmyt-2Bc,* *QGzncpk.cimmyt-3AL*	
14.	RIL (*T. spelta* (H+ 26 (PI348449) × *T. aestivum* cv. HUW 234)	Fe & Zn	*QZn.bhu-2B,* *QZn.bhu-6A,* *QFe.bhu-3B*	Srinivasa et al. (2014)
15.	DH (Berkut × Krichauff) Hexaploid (Adana99 × 70.711)	Fe & Zn	*QGfe.ada-2B,* *QGfe.ada-2B,* *QGZn.ada-2B,* *QGfe.ada-2B,* *QFe.bhu-2B*	
16.	*T. spelta* accession H + 26 (PI348449) × HUW 234			Srinivasa et al. (2014)
17.	*Hexaploid wheat (6x)* SHW-L1 × Chuanmai 32	Se		Pu et al. (2014)
18.	Seri M82 × SHW CWI76364			
19.	Tetraploid (Saricanak98 × MM5/4)	Fe & Zn	*QGfe.sar-5B&* *Qzneff.sar-6A, Qzneff.sar-6B&* *QGzn.sar-1B, QGzn.sar-6B, QGZn.sar-1B*	
20.	Saricanak98 × MM5/4 (4 × wheat)			Velu et al. (2017)
21.	DH (Berkut × Krichauff)	Zn	*QZn.bhu-1B,* *QZn.bhu-2*	
22.	Hexaploid (Adana99 × 70.711)	Zn	*QGzn.ada-6B,* *QGzn.ada-1D,* *QGzn.ada-7B*	Velu et al. (2017)

(continued)

Table 4 (continued)

S. No	Cross/parents	Traits	QTLs	References
23.	Adana99 × *T. Sphaerococcum* (70.711)			Velu et al. (2017)
24.	RIL (Synthetic hexaploid wheat × *Triticum spelta*)	Fe & Zn	*QGZn.cimmyt-7B_1P2,* *QGFe.cimmyt-4A_P2,* *QGZn.cimmyt-7B_1P2,* *QGZn.cimmyt-7B_1P1*	
25.	*Triticum dicoccon* PI94624/ *Aegilops squarrosa* [409] × BCN	Fe & Zn	*QGFe.iari-2A,* *QGFe.iari-5A,* *QGFe.iari-7A and* *QGFe.iari-7B,* *QGZn.iari-2A,* *QGZn.iari-4A,* *QGZn.iari-5A,* *QGZn. iari-7A and* *QGZn.iari-7B*	
26.	Bubo × Turtur			
27.	Louries × Batelur			
28.	Roelfs F 2007 × Chinese Parental Line			
29.	*Hexaploid wheat (6x)* Tianong18 × Limmai6	Se		
30.	WH542 × synthetic derivative (*Triticum dicoccon* PI94624/ *Aegilops tauschii* [409]//BCN). RIL (163)			
31.	Jingdong 8 × Bainong AK58			
32.	Kachu × Zinc-Shakti			

to transfer low phytic acid (LPA)-GPC in the cultivars for enhancing Fe and Zn concentration along with grain protein content without yield penalty.

Several marker-trait associations (MTAs) for nutritional traits in wheat have been used. A total of 39 Zn MTAs were discovered in two studies, one involving 330 bread wheat genotypes and the other involving 320 genotypes from the Spring Wheat Reference Set (SWRS), with two large-effect QTL regions discovered on chromosomes 2 and 7. CIMMYT developed new biofortified varieties that are 20–40% superior in grain Zn content and agronomically on par with or better than popular South Asian wheat varieties. A GWAS study for grain Zn concentrations in 369 European wheat genotypes identified 40 MTAs on chromosomes 2A, 3A, 3B, 4A, 4D, 5A, 5B, 5D, 6D, 7A, 7B, and 7D, with the important and reliable MTAs having significant effects were localized on chromosomes 3B (723,504,241–723,611,488 bp) and 5A (462,763,758–466,582,184 bp). Reported an increase in the number of MTAs to 161 genomic regions, including recently identified candidate genes for Zn uptake and transport. A GBS study on a panel of 167 Ae. tauschii accessions revealed 5249 markers, as well as wide variability in micronutrient concentrations. Overall, 19 SNP MTAs were found on all 7 chromosomes, with positive associations found for 5 with grain Fe and 4 with Zn content. These associations were found to be associated with genes that code for transcription factor regulators, transporters, and phytosiderophore synthesis. With improved genomic prediction accuracy and lower genotyping costs, genomic selection in wheat breeding has gained traction (Juliana et al. 2019; Charmet et al. 2020). In the coming years, the ability of genomic selection to increase genetic gain for quality traits will further transform wheat improvement methodologies. Genomic selection would aid in the rapid selection of desired plant types by using widely distributed markers, estimating the effects of all loci, and accurate prediction of genomic estimated breeding values with precise genotypic and phenotypic data (GEBV). Linear prediction models such as G-BLUP and machine learning algorithms are used to recognize complex data patterns and draw appropriate conclusions, as well as to exploit GxE interactions. Using multi-trait and multi-environmental models improves prediction accuracy and performance in selected breeding. Overall, genomic selection improves selection accuracy while decreasing time and cost for varietal development, particularly for complex characters with low heritability that are difficult to improve using traditional plant breeding methods (Heffner et al. 2009). An efficient genomic selection approach optimizes the statistical prediction model for developing GEBVs based solely on genotyping data for an un-phenotyped population using a precisely genotyped and phenotyped “training” population. This reduces the breeding cycle and allows breeders to dispense with avoidable multi-location and multi-environmental testing of genotypes.

When predicting the genotypic value of one panel based on another, prediction accuracy decreased. These findings are consistent with those of who demonstrated the high prediction accuracy in a germplasm set with high variation is used as training population as it has high genomic coverage. The use of efficient genomic selection models in conjunction with precision phenotyping on genetically variable populations will improve prediction accuracy, selection efficiency, and speed up the varietal development process. The addition of GWAS and genomic selection to MAS will undoubtedly shorten breeding cycles and improve the breeders’ equation. As a result, there is enormous potential for scaling up biotechnological approaches with traditional plant breeding for varietal development.

6 Role of Nanotechnology for Nutritional Improvement of Wheat

Nanotechnology has recently emerged as one of the outstanding technologies that can be gradually applied in agriculture for crop biofortification and can largely avoid the drawbacks associated with genetic and traditional agronomic biofortification. Nanomaterials have a variety of advantageous properties, including controlled and slow discharge at target sites, significantly higher absorption capacity, and a high volume to surface ratio for effective use in the production of nanofertilizers (NFs). Because nanofertilizers are used in minute quantities, they prevent the accumulation of residual by-products of chemical fertilizers in soil and thus have a lower environmental impact. Furthermore, nanofertilizers can be generated using biosensors based on soil status and crop nutritional demand.

Furthermore, NFs have been shown to improve crop performance under various stresses by modulating carbohydrate and protein synthesis, seedling growth, nitrogen metabolism, photosynthesis, and nutrient mobilization from the rhizosphere to specific plant parts. Because of its target-bound slow delivery, even a trace amount of NFs can effectively improve micronutrient levels in grain without negatively impacting the environment. Wheat, as a major staple crop, has always been a driving force behind its use in various types of biofortification and fortification. As with other biofortification strategies, a number of greenhouse or small-scale field studies show that nanomaterials have a positive effect on wheat nutritional content. Large-scale experiments in open and enclosed areas are required to assess the benefits and drawbacks of NF-based wheat nutrient enrichment. To increase the use of NFs in large-scale wheat biofortification programs, we must first understand how different nanomaterials, their combinations, and application strategies affect target nutrient levels in different wheat genotypes. Significant attention has recently been directed toward developing appropriate methodologies for applying nanoparticles, as this significantly affects the extent of micronutrient accumulation in wheat plants.

7 Role of Genome Editing Technology in Wheat Nutritional Quality Improvement

Gene editing technology has proven to be an effective tool for modifying desired traits in a variety of crop plants, including wheat. Modifying nutritional traits in crop plants provides several health benefits, particularly in staple crops like wheat. In this section, we will discuss the current progress made in the use of gene editing technology to improve the nutritional quality of wheat. Liang et al. (2017) demonstrated direct editing of the *TaGASR7* and *TaGW2* genes by introducing the CRISPR-Cas9 ribonucleoprotein complex into immature embryos of the wheat varieties Kenong 199 and YZ814. Created heritable mutations in the *TaLpx-1, TaGW2,* and *TaMLO* genes. They also demonstrated that the seed size and thousand grain weight were significantly larger (TGW). They also discovered that TaGW2 has a negative effect on grain size in wheat. In 2019, Jouanin and colleagues investigated the possibility of simultaneously editing multiple genes in the large – and – gliadin gene families.

8 Nutritional Improvement in Wheat Quality Using Genetic Engineering

Biotechnological crop improvement interventions have proven their worth for a variety of crops, including cereals, over the last 2–3 decades. Bt cotton, maize, and golden rice are a few examples. In the case of wheat, various genes determine traits such as starch composition, nutritional profile, and final end product formulation, all of which affect final grain quality. The cloning of the NAC gene *Gpc-B1* for grain protein content from this accession's chromosome arm 6BS encodes a transcription factor that accelerates senescence in plant vegetative parts, resulting in increased nutrient mobilization and mineral (iron and zinc) transfer to the grain (Shewry 2009). This could help in the fight against malnutrition. According to USDA World Wheat Collection research, the protein content of wheat grain can range from 7 to 22%, with 33% controlled by genomics and the rest by environmental factors, making breeding for this trait difficult (Vogel et al. 1978). This bottleneck can be circumvented by incorporating sources of variation from exotic bread wheat lines or related wild species, such as Atlas 50 and Atlas 66, which are derived from the South American line Frandoso. Both lines appeared to have multiple genes for high protein content in grain and have been extensively used in Nebraska breeding programs. Johnson et al. (1985) successfully inserted the Atlas 66 gene into the commercial variety Lancota (Johnson et al. 1985; Shewry 2009).

Biotechnological interventions have been attempted to increase grain starch while also modulating its quality (Borisjuk et al. 2019). *TaRSR1*, a wheat homolog of Rice Starch Regulator (*OsRSR1*), is a transcription factor that negatively regulates the gene expression pattern of some starch synthesis-related enzymes in wheat grains. Downregulation of *TaRSR1* resulted in a nearly 30% increase in starch content and a 20% increase in yield (Kang et al. 2013). Increased amylose in starch contributes to resistant starch (RS) in food, which can offer protection from health conditions such as diabetes, obesity, and cardiovascular diseases, many of which are chronic diseases (Borisjuk et al. 2019; Meenu and Xu 2019). A number of experiments focused on downregulation of starch branching enzymes SBEIIa and SBEIIb, leading to substantially elevated levels of amylose and resistant starch in wheat, which could benefit human health viz. obesity (Vetrani et al. 2018).

The level of free amino acids in wheat was significantly altered when the GCN2-type protein kinase gene was overexpressed. In another experiment, the pA25-TaGW2-RNAi DNA construct was implanted into the immature embryos of the wheat variety 'Shi 4185,' resulting in *TaGW2* gene suppression and increased grain weight and width. Using *Pina-D1a* and *pinb-D1b* genes, indicated the interaction of *PINA* with *PINB* to form friabilin which ultimately modulate the wheat grain texture.

Aggarwal et al. (2018) created a TaIPK1:pMCG161 RNAi construct that was then mobilized into C306 wheat genotypes. The transgenic lines reduced phytate by 28–56%, increasing the molar ratios of iron: phytic acid and zinc: phytic acid. Similarly, demonstrated a reduction in phytate of 22–34% using the TaABCC13: pMCG161 RNAi construct. Furthermore, several genes for Fe and Zn homeostasis in wheat have been identified, which are associated with four key pathways: the methionine cycle, phytosirophore biosynthesis, the transport system, and the antioxidant system. These genes could be used for gene editing or genetic engineering to increase the amount of Fe and Zn in wheat grain and its bioavailability. In general, there is ample scope to improve wheat nutritional quality components using modern approaches to improve the quality standards of commercial wheat.

9 Conclusion and Future Perspectives

Wheat grain contains various compounds which have potential nutraceutical functions. Wheat nutritional properties can be exploited in variousforms to prevent malnutrition and deadly diseases. For instance, wheat brans are the rich sources of flavonoids, phenolic acids, tocopherols, lignans, phytosterols, and carotenoids, which provide many health benefits. Wheat products contain a variety of high-value compounds, mainly bioactive compounds with significant health benefits. They can be exploited as food ingredients, supplements, additives, or extracts that are high in functional molecules and micronutrients, such as zinc, iron, and manganese, phenolic compounds, novel carbohydrates, carotenoids, biopeptides, bioactive fatty acids, amino acids, prebiotics, vitamins, and mineral elements. Bioactive compounds derived from wheat can be used as antioxidants and preservatives, reducing lipid oxidation and microbial growth. Furthermore, processing technologies to improve nutritional characteristics and sensory features also been targeted to increase the functional food value, and nutrients bioavailability, while reducing the anti-nutritional factors of cereal by-products. In the near future, more studies are necessary on the nutraceutical properties of wheat including bioactive compounds for use as nutraceuticals or as ingredients in the development of functional products. Some of these traits can be integrated in the wheat breeding activities as it is a key set of characteristics for the trading and commercialization of the grain. Grain nutritional quality should be an integral part of the breeding process and considered within the variety development process to deliver new products with better nutritional properties to consumers.

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