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Developing Germplasm and Promoting Consumption of Anthocyanin-Rich Grains for Health Benefits

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Malnutrition, unhealthy diets, and lifestyle changes are the major risk factors for overweight and obesity-linked chronic diseases in humans adversely impact achieving sustainable development goals. Colored grains are a source of anthocyanins, a group of flavonoids, that contribute positively to human health. This review focuses on genetic variation harnessed through breeding and biotechnology tools for developing anthocyanin-rich grain crops. Agronomic practices, genotype × environment interactions, different stresses, seed development and seed maturity are factors that impact the content and composition of anthocyanins. Significant progress has been made in characterizing genes associated with anthocyanin biosynthesis in cereal and other crops. Breeding has led to the development and release of grain anthocyanin-rich crop cultivars in Europe, America and in some countries in Asia. Notably, genetic engineering utilizing specific transcription factors and gene editing has led to the development of anthocyanin-rich genetic variants without any significant yield penalty. A variety of food products derived from colored grains or flours are now available in grocery stores and supermarkets worldwide. The public perception about anthocyanin-rich food is positive, but availability, affordability, and willingness to pay a higher price than before limit consumption. Together with other seed nutrition traits in breeding programs the inclusion of anthocyanins can ensure the development of cultivars that meet nutrition needs of humans, especially in the developing world.

Keywords: food bioactives, malnutrition, human health, biotechnology, cereal crops

OVERWEIGHT AND OBESITY, THE PREDOMINANT CAUSE OF CHRONIC DISEASES IN HUMAN

Overweight and obesity are the major risk factors associated with chronic diseases (for instance, cardiovascular disease, cancer, and diabetes). Cereals are the main source of dietary energy, essential proteins and micronutrients, vitamins, and diverse non-nutrient phytochemicals (bioactive compounds). Consumption of dietary fiber and phytochemicals in whole cereal grains contributes positively to combating chronic diseases. Bioactive compounds in phytochemicals have antioxidant, anticarcinogenic, anti-inflammatory, and antimicrobial properties. Undernutrition and micronutrient deficiencies afflict the developing world where healthy diets are not always affordable. Moreover, obesity and chronic diseases continue to rise worldwide among individuals, households, regions, nations, and continents. Cereal crops pyramided with dense nutrients and phytochemicals hold great promise to meet the growing demand of nutritionally limited populations to achieve sustainable nutrition security (Yu and Tian, 2018).

Food systems include the interactions between agriculture and human health through nutrition. Multi-dietary components of cereals have promise to overcome undernutrition (micronutrient malnutrition, overweight/obesity, chronic diseases) while such a food system research approach from farm to metabolism toward promoting human health and physiological processes is important (Bach Knudsen et al., 2017; Poole et al., 2021a,b). The evidence to date suggests that a cause-effect relationship between regular intake of anthocyanin-rich food and management of overweight and obesity to reduce the risk of chronic diseases seems promising (Araki et al., 2021; Park et al., 2021; Tian et al., 2021; Xu et al., 2021; Zhao et al., 2021; also see **Table 1**).

Anthocyanins and anthocyanidins are plant pigments. The basic core structure of both the compounds is ionic flavylium (2-phenylchromenylium). Anthocyanin is a water-soluble vacuoles pigment whereas anthocyanidin is the sugar-free counterpart of anthocyanin. Anthocyanins are the largest group of water-soluble pigments found in plant vacuoles that display a range of red, purple, black or blue colors in grains, fruits, and vegetables. Anthocyanins derived from anthocyanidins are the glycoside-form of anthocyanidin, whereas anthocyanidins are aglycones. Anthocyanins esterified with one or more acid groups are referred to as acylated anthocyanins. There characterization as acylated or non-acylated anthocyanins is based on the presence or absence of acyl group. Acylated anthocyanins are further classified as mono-, di-, tri-, and tetra-acylated anthocyanins. The color and stability of anthocyanins depend on pH, light, temperature, and structure. Anthocyanins in acidic condition are red but when pH is increased, they turn blue (Khoo et al., 2017; Vidana Gamage et al., 2022). Differences in pH (1, 3, 5, 7, 9, 11, 13), temperature (5 and 30°C), and exposure to light have been used for measuring stability of anthocyanins (Hu et al., 2014). The acidic conditions favor stability, while as when pH of the solution is increased, anthocyanins became unstable. The acylated anthocyanins are more stable than non-acylated anthocyanins. Anthocyanins with powerful radical scavenging activity display stronger antioxidant capacity. The structures of aglycone and acyl group greatly affect the stability and antioxidant capacity of anthocyanins. Both acylated and non-acylated forms of anthocyanins are present in grains, fruits, and vegetables (Vidana Gamage et al., 2022).

The focus of this review is on variable anthocyanin germplasm, their basis of inheritance, identification of their candidate genes, related single nucleotide polymorphisms (SNPs), and development of anthocyanin-rich cereal grains by crossbreeding including biotech-aided approaches. In addition, the effects of environment and cultivation practices on anthocyanin content and composition, model food for assessment of diet-health complexities, as well as their acceptance by consumers' and affordability as food are highlighted.

FACTORS AFFECTING THE CONTENT AND COMPOSITION OF ANTHOCYANIN

Cultivation practices, agroecological differences, abiotic stress, and plant development (particularly the reproductive stage, seed development and maturity) impact in anthocyanin metabolism in plants. Anthocyanin content in the seed of purple waxy maize "Heukjinjuchal" during grain filling increased while the seed color darkened. The relative composition of the anthocyanins varies with the developmental stage. Cyanidin-3-O-glucoside can range from 57 to 409 mg kg^{-1} in freshly harvested seed and 1,027 mg kg^{-1} in dry seeds, while pelargonidin-3-β-O-glucoside and malvidin-3-β-O-glucoside are detectable at 21 days after silking (DAS) (Kim et al., 2020). Maize harvested after 26 and 29 DAS of "Heukjinjuchal" had the highest concentration of amino acids and anthocyanins, respectively (Kim et al., 2020). Maximum anthocyanin concentration (51 mg g^{-1}) was detected at 23 to 28 DAS in "super sweet sweetcorn." The pigment coverage across the pericarp progressively increased from a small spot at the stigma end of the kernel to gradual spread over the entire kernel (Hong et al., 2020). A comparative study involving black seeded rice mutant "9311*bk*" and its wild type (WT) revealed significantly greater anthocyanin levels in "9311*bk*" than the WT. In another study, anthocyanin accumulation in "9311*bk*" increased progressively along with seed development, with the highest level found at seed maturity (Zaidi et al., 2019). On the other hand, early harvest of anthocyanin-rich purple wheat yielded 39% more anthocyanins than at normal harvest (Bustos et al., 2012). Assessing the effect of source-sink ratio and grain position in ear head of purple wheat revealed reduced anthocyanin content in grains at distal positions, while a higher source-sink ratio also increased anthocyanin content, largely due to differences in physiological maturity (Bustos et al., 2012).

Differences in environments due to variation in light intensity, photoperiod, temperature, soil fertility or moisture levels impact anthocyanin content in plants. Genotype, location, and genotype × location were found to significantly affect the content and composition of anthocyanins in wheat (Abdel-Aal et al., 2016). High temperature led to decreased anthocyanin levels in black seeded rice or purple skin- and fleshed-potato by ∼12% (Zaidi et al., 2019). Abiotic stresses, including cold, drought, heat, salinity, shading, and light intensity increased anthocyanins to varying levels in colored-grain rice and wheat (Chunthaburee et al., 2015; Li et al., 2018a), while heat stress increased anthocyanins in purple wheat (Hosseinian et al., 2008; Li et al., 2018a). Fertility levels, particularly N, Zn, or Mn application, have been shown to affect anthocyanin content. For example, appropriate dose of N and Zn fertilizers increased grain yield and anthocyanins in purple grain rice (Fongfon et al., 2021). Blue wheat accessions had higher content of anthocyanins across all N levels, while purple wheats accumulated significantly higher anthocyanin content under low N stress (Fan et al., 2020). The application of N fertilizer,

TABLE 1 | Description of health promoting properties of anthocyanin-rich food on humans.

Investigation	Beneficial effect on human health	References
Randomized controlled trials (RCT)	Intake of anthocyanin-rich blueberries may reduce the acute cardiometabolic burden of energy-dense meals	Curtis et al., 2022
RCT	Anthocyanin supplementation (80–320 mg day^{-1}) improve serum HDL-C levels and HDL-induced cholesterol efflux capacity (CEC)	Xu et al., 2021
RCT	Dose-dependent reduction in plasma (Cer 16:0, Cer 18:0) after 12-week anthocyanin intervention, with improvements in plasma lipids and CEC in the dyslipidemia	Zhao et al., 2021
RCT	Foods containing mainly unmethylated anthocyanins may improve glucose and lipid metabolism more effectively than those containing methylated anthocyanins	Araki et al., 2021
RCT	Anthocyanin supplementation (300 mg day^{-1}) or less for four weeks reduces BMI and BW	Park et al., 2021
Double-blind, randomized, control trial	Anthocyanin supplementation reduces platelet function in individuals with dyslipidemia	Tian et al., 2021
Zucker diabetic fatty rate	Alternation in plasma metabolites of the key pathways related to energy metabolism and insulin sensitivity	Chen et al., 2020
Mice	Incorporation of black wheat in the diet prevents obesity and metabolic complications	Sharma et al., 2020b
Preclinical, *in vitro*, *in vivo*, clinical trials	Preventive effects of anthocyanins on cardioprotection, neuroprotection, antiobesity, antidiabetes, and anticancer effects	Salehi et al., 2020
RCT on healthy humans	Extract from anthocyanin-rich purple potatoes lowered postprandial glycemia and insulinemia, and affects postprandial inflammation on human	Jokioja et al., 2020
Overweight volunteers	Intake of bilberry anthocyanin extract reduces postprandial glycaemia without changes in insulin due to reduced rates of carbohydrate digestion and/or absorption	Alnajjar et al., 2020
In silico	Anthocyanin extract from blue maize and black bean provides antidiabetic benefits	Damián-Medina et al., 2020
Epidemiological, clinical, animal model	Positive roles of dietary anthocyanins in preserving cardiovascular health	Krga and Milenkovic, 2019
RCT	Supplementation with anthocyanin have beneficial effect on HOMA-IR in adults	Daneshzad et al., 2019
–	Beneficial effect of anthocyanins in obesity-associated inflammation and changes in gut microbiome	Jayarathne et al., 2019
Danish Cohort	Moderate intake of flavonoids inversely associated with reduced mortality due to cancer and cardiovascular vascular diseases	Bondonno et al., 2019
Mice, pig	Presence of parent anthocyanins in animal model (mice, pig) tissues means it may role in human health	Sandoval-Ramírez et al., 2018
Longitudinal analysis involving 839 subjects	Significant inverse associations between anthocyanin intake and age-related decline in lung function	Mehta et al., 2016
RCT	Anthocyanins and anthocyanin-rich extract may decrease LDL cholesterol among individuals with elevated CVD markers	Wallace et al., 2016
C57BL/KsJ *db/db* mice	Anthocyanin-rich purple maize extract ameliorated hyperglycemia and hyperlipidemia by reducing the blood glucose levels and increasing the serum insulin	Huang et al., 2015
In vitro cell culture and *in vivo* animal model	Positive effect of anthocyanin-enriched purple-fleshed sweetpotato diet on prevention of colorectal cancer	Lim et al., 2013

however, is beneficial to maximize productivity of modern wheats harboring "Green Revolution" genes. Magnesium fertilization increases anthocyanin content (Bustos et al., 2012) and ameliorates the deleterious effect of elevated temperature on anthocyanins (Guo et al., 2016; Ciscomani-Larios et al., 2021). Likewise, the interaction between anthocyanin biosynthesis genes and abiotic stresses on one hand and variation in daily and seasonal rhythms in response to differences in temperature, light, humidity, and precipitation on the other have profound effects on phytochemical composition in plants (Azuma et al., 2012; Li et al., 2018a; Liebelt et al., 2019; Saad et al., 2021). Thus, understanding how phytochemical composition varies based on time is critical to unlock underlying regulatory connections to improve the quality of phytochemical compounds (Liebelt et al., 2019).

Clearly, environment, genotype × environment interaction, and abiotic stresses affect the content and composition of anthocyanins. Therefore, multi-site testing across diverse agro-ecologies is recommended to identify stable and anthocyanins-rich germplasm for use in crop breeding and to identify sites more favorable for production of anthocyanins-rich crops.

SOURCES OF VARIATION, COMPOSITION AND STABILITY OF ANTHOCYANINS

Germplasm is the main source for crop improvement programs because it represents a large pool of genetic diversity. Researchers can use it to draw allelic variation for developing new cultivars with significant nutrient and health benefits.

Anthocyanin-Rich Tissues in Grains

A variety of grain colors (purple, blue, black, and white) of anthocyanins have been observed in barley, rice, and wheat, with white or brown grains being predominantly used for food purpose. Both maize and sorghum have a variety of seed colors from black, blue, brown, and pink to purple and red. Anthocyanins are localized in outer layers of the grains, for example, anthocyanin in purple grains is localized in pericarp while in blue grains it is localized in aleurone layer. Both aleurone and pericarp layers contain anthocyanins in black or red grains (Abdel-Aal et al., 2012; Francavilla and Joyé, 2020).

Variability

Table 2 summarizes various reports that have revealed multi-fold differences for anthocyanin content in grain crop germplasm. Colored-seeded (black, blue, purple) barley germplasm was found to have substantial variation in anthocyanin content (13–1037.8 $\mu g\ g^{-1}$ dry weight, DW), with purple and blue barley containing on average higher anthocyanin content than black barley. Predominant anthocyanin in the purple barley is cyanidin 3-glucoside, whereas in the blue and black barley it is delphinidin 3-glucoside (Kim et al., 2007). Hull-less barley grains (known as "qingke" in Chinese) is a valuable food in Tibet. Tibetan Qingke cultivars (black, blue, white) differ substantially in total phenolics, flavonoids, proanthocyanidins, anthocyanins, and antioxidant capacity. "Black Qingke" cultivar has highest concentrations of these compounds followed by blue and white Qingke cultivars (Lin et al., 2018). In purple qingke (POK) and black qingke (BOK) cultivars, six anthocyanins with most acylated types have been reported. The total anthocyanin content in POK and BOK ranged from 14 to 2,304 $\mu g\ g^{-1}$ and 248.7 to 2,902.9 $\mu g\ g^{-1}$ DW, respectively (Zhang et al., 2021).

TABLE 2 | Natural genetic variation for total anthocyanin content in barley, maize, rice, sorghum, and wheat germplasm pools.

Crop	Fold-difference and range variation	References
Barley	16-, and 80-folds (0.14–2.30, 0.013–1.038 mg g^{-1} DW)	Kim et al., 2007; Zhang et al., 2021
Maize	6-, 11-, 12-, 15-, and 54-folds (0.398–2.398, 0.023–0.252, 0.047–0.595, 0.07–1.06, 0.0138–0.7452 mg g^{-1} DW)	Harakotr et al., 2015; Nankar et al., 2016a; Paulsmeyer et al., 2017; Rodríguez-Salinas et al., 2019; Mendoza-Mendoza et al., 2020
Rice	9-, 14-, 25-, and 12-folds (0.298–2.758, 0.21–2.98, 0.68–17.3, and 0.27–3.276 mg g^{-1} DW)	Abdel-Aal et al., 2006; Chen et al., 2012, 2017; Bhuvaneswari et al., 2020
Sorghum	21-fold (0.032–0.68 mg g^{-1} DW)	Dykes et al., 2009
Wheat	9-, and 22-folds (0.10–0.88, 0.0034–0.0752 mg g^{-1} DW)	Eticha et al., 2011; Böhmdorfer et al., 2018

Original data were converted into mg g^{-1} dry weight, DW.

Landraces are dynamic population(s) of a crop that have a historic origin and distinct identity that was locally adapted in association with traditional farming systems. The maize landrace (conical cob) from San Juan Ixtenco, "Tlaxcala," Mexico represents an important genetic resource rich in bioactive compounds (Mendoza-Mendoza et al., 2017). This type of maize has a high capacity to synthesize and accumulate anthocyanins both in the corncob and the kernel. The pericarp has the highest concentration of anthocyanins (0.2529–2.6452 g 100 g^{-1} DW) followed by the cob (0.1004–1.1022 g 100 g^{-1} DW), kernel (0.0398–0.2398 g 100 g^{-1} DW), and the aleurone layer (0.0044–0.0523 g 100 g^{-1} DW), respectively (Mendoza-Mendoza et al., 2020). Anthocyanin content in some populations, particularly those with dark color of the kernel and corncob, surpassed the quantity of anthocyanins in the best-known Peruvian purple maize.

Comparative profiling of colored-grain Mexican maize landraces indicated presence of 18 different anthocyanins with cyanidin-based anthocyanins being predominant in dark purple and pelargonidins in red-pink kernels (Peniche-Pavía and Tiessen, 2020). Anthocyanin content was highest in pericarp-pigmented accessions with flavanol–anthocyanin condensed forms, similar to the Andean "Maiz Morado" landraces (Paulsmeyer et al., 2017). Among US southwestern blue maize landraces, five-fold differences averaged across locations 0.43 g kg^{-1} kernel tissue, with "Santa Clara Blue," "Yoeme Blue," "Ohio Blue," and "Hopi Blue" in the range between 0.52 and 0.58 g kg^{-1}. The predominant anthocyanins were cyanidin 3-glucoside, pelargonidin and peonidin 3-glucoside (Nankar et al., 2016b). "Millo Corvo," an ancient-colored landrace from Galicia (Spain), is a good source of high amounts of anthocyanins (83.4 mg 100 g^{-1} flour), particularly predominant in cyanidin (Lago et al., 2015). Traditional farmers in the USA and Mexico borderland region cultivate many types of maize landraces with diverse kernel characteristics reflecting their enculturated preferences. Assessment of 48 diverse accessions of 18 maize races originating from this borderland region indicated a wide range of variation in grain anthocyanin content across and within populations, some with anthocyanin concentration above 50 mg $100g^{-1}$ (Ryu et al., 2013). Accession refers to a distinct, uniquely identifiable sample of seeds representing a cultivar, breeding line or a population.

Colored maize grains, preferably blue or purple, are often used to prepare traditional and diverse dishes in Mexico. Assessment of pigmented maize landraces in Mexico revealed that magenta colored maize grains contain anthocyanins in the pericarp and the aleurone layer, while blue and purple maize grains are found in the aleurone layer. The total anthocyanin content in magenta grains was up to 10-fold greater than blue or purple grains with 9–11 anthocyanin derivatives: cyanidin, peonidin and pelargonidin, being the major anthocyanins. The blue and purple maize grains have similar profiles to magenta grains with predominantly mono acylated derivatives of cyanidin (Salinas-Moreno et al., 2013). Among the pigmented native landraces (Olotillo, Olotón, Tehua, Tepecintle, Tuxpeño, Vandeño, Zapalote Grande) of maize in Mexican province of Chiapas, blue-grain types were the most common followed by light red and purple reddish types. Blue- and red-grain type races had highest (213.6–904.0 mg of cyanidin 3–glucoside equiv/kg of sample) and lowest (30.7–188.1 mg of pelargonidin chloride equiv/kg of sample) range variation for anthocyanin content, respectively. Of these, Olotillo could be a better choice for preparation of food products because of its high anthocyanin content together with hard texture (Salinas-Moreno et al., 2012).

Rice germplasm from South and Southeast Asia have multi-fold differences in anthocyanins (Chen et al., 2012; Hosoda et al., 2018). Cyanidin 3-glucoside, peonidin 3-glucoside, cyanidin diglucoside, and malvidin are the predominant anthocyanins in black- and red-seeded rice. Aromatic rice "Chakhao" from the northeastern Indian state Manipur is a speciality glutinous rice. Molecular analysis of "Chakhao" landraces differing in seed color (purple and non-purple) grouped 93 accessions into three subpopulations, with deep purple type forming a distinct cluster. The predominant anthocyanins were cyanidin 3-O-glucoside and peonidin 3-O-glucoside (Bhuvaneswari et al., 2020).

Anthocyanin content among 25 sorghum assessions differing in pericarp pigments varied from 575 to 1,461 g kg^{-1} seed. The red and brown pericarp accessions PI297139 and PI221723, respectively, had the highest amounts of anthocyanins: 1,461 and 1,376 g kg^{-1} seed with 3-deoxyanthocyanidins being predominant (Su et al., 2017).

Introgression refers to the transfer of genetic information from one species to another *via* hybridization between them and repeated backcrossing. Purple- and blue-grain wheat germplasm, the former from a tetraploid wheat from Ethiopia and the latter from the introgression of a diploid wheat with *Agropyron elongatum* resulted in both purple and blue grains in hexaploid wheat (Zeven, 1991). Comparative assessment of black, blue and purple wheat germplasm from India revealed delphinidin-3-o-galactoside, delphinidin-3-o-glucoside, and cyanindin-3-o-glucoside as major anthocyanins (Sharma et al., 2020a). Significantly higher anthocyanin content was detected in gamma rays-induced mutants (L47, L167, L925) than WT, while K4191, a purple-seeded wheat germplasm, and L925 having highest total anthocyanin content with cyanidin-3-glucoside being the most predominant anthocyanin (Hong et al., 2019). The evaluation of 76 durum and bread wheats for over three seasons revealed that blue-aleurone bread wheat germplasm contains higher anthocyanins than purple- and red-pericarp durum wheats, with 5–8 major anthocyanins in blue-wheat extract and three-anthocyanins in purple and red wheats. Delphinidin 3-O-rutinoside, delphinidin 3-O-glucoside, and malvidin 3-O-glucoside were predominant in blue wheat and cyanidin 3-O-glucoside, peonidin 3-O-galactoside, and malvidin 3-O-glucoside in purple wheat (Ficco et al., 2014). **Supplementary Table 1** contains a few germplasm lines (cultivar, breeding lines, genetic stocks, landraces, cultivars) with highest and lowest anthocyanin contents which are useful in breeding and genetics of anthocyanin in barley, maize, rice, sorghum, and wheat. Genetic stocks represent a unique germplasm (cytological stocks, mutants, germplasm sets) of either transient or long-lasting value. Cultivar refers to a cultivated variety; selected and cultivated by humans, while in nature, population of plants within a species differs in some significant way from other members of that species, is known as a variety by botanist. Advanced lines originating from crossbreeding are designated as breeding lines.

Composition, Stability, and Nutritional Quality

Assessing the composition, stability and profiling of colored grains is critical for consumption of anthocyanin-rich foods. Metabolite profiling of hull-less barley cultivars differing in grain colors presented 608 metabolites. Among these ABC transporters, flavonoid biosynthesis and anthocyanin biosynthesis pathways were found to be the predominant metabolic pathways. Colored barley cultivars clustered distinct from white barley (Liang et al., 2021).

Total anthocyanin content in pericarp and aleurone layer among four native maize landraces from "Arrocillo," "Cónico," "Peruano," and "Purepecha" ranged from 54 to 115 mg 100g^{-1} DW, with similar anthocyanin profiles but differing in relative percentages (Salinas-Moreno et al., 2005). Biochemical attributes of blue and purple maize landraces of southwestern United States revealed that a majority of blue landraces had higher oil and protein contents, while a few were richer in lysine and methionine than the open pollinated variety (OPV) (Nankar et al., 2016a). OPV refers to a type of cultivars originated from open pollination of a set of individuals possessing high genetic diversity, which enable such OPV to adapt to diverse environments. The pericarp-pigmented maize cultivars contain cyanidin-derived anthocyanins that produce blue, red or pink extracts. Maize lines derived from landrace Apache Red (AR) predominantly contained pelargonidin-derived anthocyanins in the pericarp (Chatham et al., 2018). Two new flavanol-anthocyanins, catechin-(4,8)-pelargonidin 3,5-diglucoside and afzelechin-(4,8)-pelargonidin 3,5-diglucoside, in addition to several apigenin-derived C-glycosyl flavones in abundance were also identified. These findings suggest that AR is an important genetic resource for studying flavonoid biosynthesis pathway.

In amber and pigmented (black, red) rice grains about 110 metabolites were found, with black and red rice containing greater levels of flavonoids. Black rice also contained high levels of carotenoids, tocopherols, phytosterols, and monoterpenes, while non-pigmented grains were low in secondary metabolites. The metabolite clusters were based on N and C sources, with black rice rich in C-based secondary metabolites and low in primary metabolites compared with other rice grains. The complex interactions between C and N metabolism of primary and secondary metabolites may contribute to developing new rice cultivars with specific metabolites (Kim et al., 2021).

In advanced breeding lines derived from crosses involving exotic donor lines (blue or purple grains), 22, 23, and 26 different anthocyanins were present in blue, purple and black wheat grains, respectively, with anthocyanin content ranging from 16 to 198 mg kg^{-1} grains (Garg et al., 2016). The blue ("Skorpion") and purple ("Jakubz") wheat cultivars contained 19 and 26 anthocyanins each, with former containing 9.26 mg kg^{-1} and the latter 13.23 mg kg^{-1} of total anthocyanins (Bartl et al., 2015). Cyanidin 3-glucoside, cyanidin 3-rutinoside, and peonidin 3-rutinoside were present in both wheats; while delphinidin 3-glucoside and delphinidin 3-rutinoside were present only in blue wheat; and pelargonidin 3-glucoside, pelargonidin 3-rutinoside, and peonidin 3-glucoside present only in purple wheat.

The profiling of anthocyanins in processed bran fraction of purple wheat identified a complex of 5 pigments, including cyanidin 3-glucoside, cyanidin-3-(6-malonyl glucoside), cyanidin 3-rutinoside, peonidin 3-glucoside, and peonidin-3-(6-malonylglucoside), which contributed to 93–96% of the total anthocyanins. Purple wheat bran and its powder both were found to have higher antioxidant activity (Abdel-Aal and Rabalski, 2018).

Assessment of 26 pigmented native maize populations of Mexico revealed that "EO22" and "Pep20" were superior for large grains (44.84 g 100 $seeds^{-1}$) and high-quality protein (protein: 9.58%; protein quality index: 0.814), tryptophan (0.0765%), and anthocyanins (276.58 mg cyanidin 3-glucoside kg^{-1} dry matter) (Rojas et al., 2019). The pigmented native landraces from Northeast of Mexico differed in color parameters (L*, C*, h:25.13–63.64, 2.41–33.58, 14.36–359.19, respectively) and richer in carbohydrates (71.30–74.88), protein (9.72–12.57), P (334–720 mg 100 g^{-1}), K (314–397 mg 100 g^{-1}), Mg (116.24–146.75 mg 100 g^{-1}), Zn (2.8–4.5 mg 100 g^{-1}) and Fe (0.77–2.53 mg 100 g^{-1}) (Rodríguez-Salinas et al., 2019).

Flour of purple grain of an Abyssinian wheat landrace from Ethiopia was found to contain 197 mg 100 g^{-1} anthocyanins together with a distribution of 5.5% ash, 8.5% protein, 3% fat, 7.3% fiber, and 64.8% carbohydrates (Kassegn, 2018). The pigmented and amber (white) wheat had no major differences in nutritional and processing characteristics related to end use quality, but colored wheats had higher protein content and dietary fibers (Kumari et al., 2020), and higher iron and zinc content (Sharma et al., 2018). A wheat-*T. boeoticum* introgression line Z18-122 that originated from a cross between G52 (*T. boeoticum*) and Crocus (wheat) had, on an average, a slightly lower (67.24 μg g^{-1}) content of anthocyanins than in G52 (72.31 μg g^{-1}) but significantly higher than that in Crocus (7.81 μ g^{-1}). The essential amino acid content was 48% higher than Crocus (16.16). Zn and Fe contents were 39% (74.5 mg kg^{-1}) and 109% (109.7 mg kg^{-1}) greater than Crocus (Zn, 52.4 and Fe 53.9 mg kg^{-1}) (Liu et al., 2021a). Thus, cultivated gene pools contain usable genetic variation for anthocyanin content and composition and could be explored for developing anthocyanin-dense cereal grains. Gene pool refers to the stock of different genes in an interbreeding population, broadly grouped as primary (members intermate freely within the species), secondary (members closely related with cultivated species, can cross and produce at least some fertile hybrids), and tertiary (distantly related to the members of the primary gene pool; could be intermated with primary gene pool by using *in vitro* techniques to rescue F_1 due to lethality and physiological abnormality of complete sterility or bridging species) gene pool.

FUNCTIONALLY CHARACTERIZED AND PUTATIVE CANDIDATE GENES

Understanding the genetic and molecular basis and identification of genetic tags (DNA markers) associated with trait expression offers great promise to enhance crop breeding efficiency. A candidate gene is a gene identified by its position in a chromosome that relates to trait expression; however, such candidates need to be functionally validated prior to being deployed in crop breeding practices. Functionally characterized genes and those recently discovered "candidate" genes are discussed in this section (**Table 3**). Transcriptional regulation of anthocyanin biosynthesis involves DNA-binding R2R3 MYB factors, MYC-like helix-loop-helix, and WD40-repeat proteins (Allan et al., 2008; Matus et al., 2008; Hichri, 2010). Specificity of DNA-binding of MYB proteins and, in some instances, bHLH proteins activate subset of genes. WD40-repeat proteins have mostly a general role along the regulatory complex (Hichri, 2010). Additional insights into anthocyanin biosynthesis regulation have also been provided (Jaakola, 2013).

Anthocyanins in the aleurone layer cause "blue" grain barley, while in the pericarp they account for purple or red barley (Lundqvist et al., 1997). The black pericarp gene (*Blp*) was mapped between the Indel markers MC_1570156 and MC_162350, with a physical distance of 0.807 Mb and contained 21 annotated genes on chromosome 1H. The sequencing of black and yellow barley led to discovering candidate genes associated with *Blp* (Long et al., 2019). Five structural (*F3′M*, *HID*, *UF3GT*, *UFGT*, *5MAT*) and one regulatory (*Ant1*) genes conferred purple seed coat color to hulless barley (Yao et al., 2018). Blue grain barley complementary genes include *Blx1*, *Blx3* and *Blx4*, which are intricately linked to one another and clustered on chromosome 4HL, with *Blx2* and *Blx5* on 7HL (Finch and Simpson, 1978). A regulatory complex of MYB–bHLH–WD repeat (MBW) transcription factors (MYB, bHLH/MYC, WD40) and genes *HvMyc2* and *HvMpc2* on chromosome 4HL and *HvWD40* on 6HL regulate anthocyanin synthesis in barley aleurone layer. MBW complex is a highly conserved transcriptional complex model. It regulates WRKY protein control of the flavonoid pigment pathway in plants (Lloyd et al., 2017). The expression of *HvMyc2* is confined to aleurone cells but not the non-colored aleurone tissue. Both the genes have been genetically mapped between microsatellite loci XGBS0875-4H (3.4 cM distal) and XGBM1048-4H (3.4 cM proximal) on 4H, where in the *Blx*-cluster was discovered. The anthocyanin biosynthesis structural gene *HvF3′5′H* (Strygina et al., 2017) was also mapped at this position. A trigenic cluster MbHF35 including *HvMYB4H*, *HvMYC4H* and *HvF35H* genes in *Blx1* locus mapped to ∼1.13Mb genetic interval on chromosome 4HL and confers blue color to barley grains (Jia et al., 2020). *HvnHID* from hull-less purple grain Tibetan barley "Nirumuzha" has also been isolated (Yao et al., 2022). The expression of key genes (*HvnF3'H*, *HvnDRF*, *HvnANT1*, *HvnGT*)

TABLE 3 | Candidate or functionally characterized genes regulating anthocyanin biosynthesis in barley, maize, rice, and wheat.

Gene	Description	References
HvnHID	Negatively regulates anthocyanin biosynthesis in a purple grain color in hullless barley "Nirumuzha"	Yao et al., 2022
TbMYC4A	Confers blue aleurone trait in wheat-*T. boeoticum* substitution line	Liu et al., 2021a
TraesCS1D02G019200; *TraesCS2A01GS27700;* *TraesCS6B01G006200*	The former core regulatory and the latter two structural genes, critical to anthocyanin biosynthesis in wheat	Wang et al., 2021
Ant1	Overexpression of *Ant1* resulted increased accumulation of anthocyanin in the pericarp and aleurone layer of transgenic barley grains	Zhou et al., 2021
OsMATE34	Associated with anthocyanin transport in black rice caryopsis	Mackon et al., 2021
OrC1	Activates anthocyanin biosynthetic genes *OsCHI*, *OsF3H* and *OsANS* in rice	Qiao et al., 2021
OsTTG1	*OsTTG1*, regulator of WD40 in MBW complex, an important gene resource for the genetic engineering of anthocyanin biosynthesis in rice and in other crops	Yang et al., 2021
HvMYB4H, *HvMYC4H, HvF35H*	A trigenic cluster in *Blx1* locus mapped to ∼1.13Mb region on chromosome 4HL and confers blue colored grains in barley	Jia et al., 2020
TsMYC2	Regulates blue aleurone trait in triticale	Zong et al., 2019
Blp	Mapped to 0.807 Mb genomic region on chromosome 1H containing 21 annotated genes; *HORVU1Hr1G087010*, *HORVU1Hr1G086970*, *HORVU1Hr1G086980*, *HORVU1Hr1G087070*, *HORVU1Hr1G086920*, *HORVU1Hr1G086780* potential candidate genes in wheat	Long et al., 2019
GRMZM2G480439, *GRMZM2G130149*, *GRMZM2G147346*, *GRMZM2G084583*, *GRMZM2G070849*, *GRMZM2G325907*, *GRMZM2G001930*, *GRMZM2G380650*	Regulate anthocyanin biosynthesis in maize expressed on pericarp or aleurone layer or in both tissues in maize	Li T. et al., 2019
F3′M, *HID*, *UF3GT*, *UFGT*, *5MAT, Ant1*	Confer purple seed coat color in hulless barley; the first five structural genes and latter regulatory gene	Yao et al., 2018
OsMYB3	Higher expression of *OsMYB3* in pericarps of black rice relative to white rice and downregulation of anthocyanin metabolites in grains of knockout *OsMYB3* black rice cultivar	Zheng et al., 2021
C-S-A	*C1* and *S1* interaction activate expression of *A1* to produce purple colored seed, while loss of function of *A1* leads to a red-pigmented seed in rice	Sun et al., 2018
TaPpm1, *TaPpb1*	Coregulate purple pericarp color in wheat; *TaPpm1* widely expressed in many tissues including pericarp, while *TaPpb1* expression limited in seeds	Jiang et al., 2018
HvMyc2, *HvMpc2*, *HvWD40*	The first two mapped on chromosome 4HL and the latter on chromosome 6HL regulate anthocyanin synthesis in barley aleurone	Strygina et al., 2017
ThMYC4E	A candidate for *Blue aleurone 1* (*Ba1*) gene that regulate anthocyanin biosynthesis in blue aleurone layer in wheat	Li et al., 2017

in the anthocyanidin biosynthetic pathway were at higher level while *HvnHID* expression decreased, thereby it acts as a negative regulator of anthocyanin biosynthesis in "Nirumuzha."

Comparative transcriptome analysis of two tissues of purple grain maize lines differing in anthocyanin accumulation (Ha0414 with purple pericarp and Ha6130 with purple aleurone layer) identified, respectively, 16 and 14 differentially expressed genes associated with the anthocyanin biosynthesis pathway. Three genes increased in transcript abundance in both the colored pericarp and the aleurone layer, while two other genes increased in transcript abundance in the aleurone layer of Ha6130. Thirty-six transcription factors (TFs)—including bHLH, WRKY and HB—in the pericarp of Hao414 and 79 TFs –including MYB, MYB-related and bHLH TFs in the aleurone layer of Ha6130 with increased transcript abundance suggest tissue-specific accumulation of anthocyanins in pericarp and aleurone layer of maize grains (Li T. et al., 2019).

A *C-S-A* gene model that controls seed pigmentation was proposed in rice (Sun et al., 2018). *C1* encodes a R2R3-MYB transcription factor, *S1* encodes a bHLH protein that functions in a tissue-specific manner, and *A1* encodes a dihydroflavonol reductase. The *C1* and *S1* interactions activate expression of *A1* to produce purple colored seed containing high accumulation of cyanidin 3-O-glucoside. Loss of function of *A1* leads to a red-pigmented seed due to accumulation of hesperetin 5-O-glucoside, rutin, and delphinidin 3-O-rutinoside. Significantly higher expression levels of *OsMYB3* were found in pericarps of black rice relative to white rice while knockout of *OsMYB3* in black rice caused significant downregulation of 19 anthocyanin metabolites in grains (Zheng et al., 2021). Thus, *OsMYB3* is an determinant R2R3-MYB gene for anthocyanin biosynthesis in rice pericarps.

A multidrug and toxic compound extrusion (MATE) gene, OsMATE34, associated with anthocyanin transport in black rice caryopsis has also been identified (Mackon et al., 2021). OsMATE34 has high similarities with other anthocyanin transporter genes, VvAM1, VvAM3, MtMATE2, SlMATE/MTP77, RsMATE8, AtFFT, and AtTT12. Further analysis involving black and white caryopsis at different time intervals after flowering identified 36,079 genes, including 33,157 known and 2,922 new genes. Of these, there were 15,573 differentially expressed genes (DEGs) that were commonly expressed while 1,804 and 1,412 genes were uniquely expressed in black and white caryopsis, respectively. OsMATE34 expression is significantly upregulated in all black caryopsis but not in white caryopsis. OsMATE34 expression is like OsGSTU34, a transporter of anthocyanin in rice leaves. Thus, OsMATE34 (Os08g0562800) is a candidate anthocyanin transporter in rice caryopsis. A novel allele of chromogen (a precursor of a biochemical pigment) gene *C*, *OrC1*, associated with anthocyanin biosynthesis in *O. rufipogon* has also been cloned (Qiao et al., 2021). *OrC1* regulates flavonoid biosynthesis pathway and activates a few bHLH and WD40 genes of ternary MYB-bHLH-WD40 complex in *indica* rice. *OrC1* activates the anthocyanin biosynthesis pathway genes, namely, *OsCHI*, *OsF3H* and *OsANS*, and produces six metabolites independently.

TaPpm1 (purple pericarp-MYB 1) and *TaPpb1* (purple pericarp-bHLH 1) form a complex to co-regulate purple pericarp color in wheat. *TaPpm1* is widely expressed in many tissues including pericarp, while *TaPpb1* expression is limited to seeds (Jiang et al., 2018). Gene coexpression network analysis based on weighted gene and involving five stages of seeds development in purple wheat variety ZNM168 identified *TraesCS1D02G019200* (*TaBZ1 UniGene*) as core regulatory gene and *TraesCS2A01GS27700* (*TaCHS*) and *TraesCS6B01G006200* (*TrANS*) as structural genes critical to anthocyanin biosynthesis in wheat (Wang et al., 2021). *Blue aleurone 1* (*Ba1*) confers blue grain color to bread wheat. A comparative assessment of blue and white aleurone layer transcriptomes revealed higher level of transcripts of the bHLH TF *ThMYC4E* in the blue aleurone phenotype. It forms clusters with genes that regulate anthocyanin biosynthesis. *ThMYC4E* may be a candidate *Ba1* gene controlling the blue aleurone trait in bread wheat with an introgression from its wild relative *Th. ponticum* (Li et al., 2017). *Ba2* confers blue grain trait in *T. boeoticum*. A comparative transcriptome profiling between blue-grained wheat-*T. boeoticum* substitution line and its wheat parent identified 41 and 29 unigenes, respectively, related to anthocyanin biosynthesis and transport. *TbMYC4A* contains three bHLH TF domains (bHLH-MYC_N, HLH, ACT-like), clusters with other blue grain genes from other *Triticeae* species, and is highly expressed in the blue-grained substitution line. The *TbMYC4A*-specific marker is also present in *T. boeoticum* and *T. monococcum* with blue aleurone but not in other *Triticeae* species with white aleurone, suggesting *TbMYC4A* as a candidate gene of *Ba2* controlling the blue aleurone trait (Liu et al., 2021b). Transcriptome differences between the triticale lines HM13 (blue aleurone) and HM5 (white aleurone) revealed *TsMYC2*, a bHLH TF gene that regulates blue aleurone trait in triticale (*Secale cereale*), and which may be a good gene to be deployed to breed blue-grain triticale (Zong et al., 2019).

Clearly, significant progress has been made in identifying genes associated with anthocyanin biosynthesis in cereal crops, some of which have also been functionally characterized (**Table 3**). Functionally characterized genes and associated DNA markers may be deployed in crop breeding to select for grain-anthocyanin-rich segregants. Candidate genes can be characterized by either generating random mutants, insertion/deletion mutants (transposons), establishing mutants genetic screen, gain-of-function, or loss-of-function mutants, and microarrays-based gene expression, RNAi knockout lines, or transgene overexpression (Alberts et al., 2002), and targeted gene editing (Kamburova et al., 2017).

REDESIGNING ANTHOCYANIN-RICH STAPLE FOOD CROPS

Fixing the Biologically Attainable Target

Plant breeding has been realigning its agenda to meet end-users' demands of nutrient-rich diets (Patil et al., 2014). Crossbreeding and genetic engineering may significantly increase anthocyanins as evidenced in citrus (Rapisarda et al., 2009), potato (Stobiecki et al., 2003), tomato (Davuluri et al., 2005) and wheat (Gordeeva et al., 2020). Screening of crop germplasm (including breeding populations) often shows a significant and high heritable variation of anthocyanin content, e.g., in maize (Paulsmeyer et al., 2017) or in various fruits and vegetables (Patil et al., 2014 and references therein). However, scanty results about bioavailability are known to show that such increases lead to improving human health (Pascual-Teresa and Sanchez-Ballesta, 2008).

China has defined a daily 50 mg intake of anthocyanins as target (Wallace and Giusti, 2015) but such dietary reference is not available in North America or in Europe (Wallace et al., 2015). Moreover, the dietary intake of anthocyanins may vary according to age, ethnicity, and gender (National Center for Health Statistics, 2015). Therefore, developing a product profile is necessary for targeting anthocyanin-rich crops. The product profile for each crop states target(s) for breeding within a timeframe to develop a new cultivar showing increased bioavailable anthocyanins. The newly bred cultivar aims to replace those in use today to ensure market impacts. In this regard, the use of databases characterizing the intake of anthocyanins (Zamora-Ros et al., 2010, 2013; Sebastian et al., 2015) can assist in identifying main sources and determine their links with dietary quality and related human wellbeing. It is possible that the data may indeed show that a healthy eating index positively correlates with flavonoid intake, but this remains yet to be determined.

Crossbreeding and Genomic-Assisted Breeding

Progress achieved to date in the development and release of pigmented (purple, black, blue, or red) cereal grain cultivars is

TABLE 4 | Anthocyanins-rich grain crop cultivars or advanced breeding lines and genetic stocks developed through crossbreeding and selection in cereals.

Cultivar	Description	Reference
Barley		
NILs	Purple pericarp NILs containing *Ant1* and *Ant2* alleles developed	Gordeeva et al., 2019b
Maize		
Moradyn	An anthocyanin-rich cultivar adapted to northern Italy	Ferron et al., 2020
Purple waxy anthocyanins lines	Several high anthocyanins (22.4–260.10 μg L^{-1}) lines with reasonable grain yield (2.0–3.5 t ha^{-1}), a useful genetic resource to derive anthocyanins rich inbreds for hybrid cultivars development	Liet et al., 2018
Saekso 2	Anthocyanin-rich hybrid cultivar released in south Korea	Choi et al., 2017
Polenta	Anthocyanin-rich in the genetic background of traditional cultivar "Scagliolo" devoid of anthocyanins released for cultivation in northern Italy	Lago et al., 2014
Blue-grain hybrids	A number of productive blue-grain hybrids adapted to subtropical environments with better biophysical and nutraceutical grain traits suitable for tortilla industries	Urias-Peraldí et al., 2013
Rice		
"Pinhei 1," "Zhongi 4," "Ziyunuo," and IL in genetic background of "Koshihikari"	First three cultivars grown in People's Republic of China while the latter in Japan	Xia et al., 2021
–	Aromatic pigmented (black pericarp) *indica* lines selected through interspecific crosses involving "Badshabhog" and "Chenga" with O. rufipogon	Roy and Shil, 2021
"Chak-hao Amubi," "Chak-hao Poireiton," "Chak-hao Angangba"	Black-pigmented rice predominantly grown in northeast India	Krishnan et al., 2020
"Rubin, Yuzhnaya"	Red- and black-grain cultivars grown in some parts of Russia	Krishnan et al., 2020
"Ziyunuo"	Increasingly popular among consumers due to its color, aroma, and taste comparable to standard of black glutinous rice	Li M. et al., 2019
–	Advanced lines with high anthocyanin content selected from the cross between the black and white rice parental lines	Zhang et al., 2015
Introgression lines	6.8-fold increase in proanthocyanidins in brown and milled rice grain with excellent quality characteristics compared to recurrent parents	Sharma et al., 2014
Wheat		
"Saratovskaya 29"	A blue-grained cultivar as well several advanced lines combining resistance to diseases and purple-seed characteristics and adapted to the West Siberian region	Gordeeva et al., 2019a, 2020
"NABIMG-11-Black," "NABIMG-10-Purple," and "NABIMG-9-Blue"	Colored (blue, purple, and black) grain wheat lines, with black ones having highest anthocyanins, developed in India; "NABIMG-11-Black" gaining popularity among farmers, industry and consumers	Garg et al., 2016; Garg, 2018a,b,c
Blue-grained wheat-*Triticum boeoticum* substitution lines	Six blue-grained wheat disomic substitution lines, containing all wheat (42) and *T. boeoticum* (14) chromosomes, represent a novel germplasm resource for blue-grained wheat breeding	Liu et al., 2020
"AnthoGrain"	Developed by "Saskatchewan Wheat Pool (SWP)" and promoted for commercialization by "InfraReady" in Canada during mid-1990s; later another purple wheat "CDC Primepurple"	https://www.topcropmanager.com/new-possibilities-with-purple-wheat-20050/

summarized in **Table 4**. A multi-season trial noted significant differences for agronomic and phytochemical traits among advanced barley cultivars having hull-less pigmented grains. Cluster analysis separated barley cultivars into three groups: with L1997, L3005, L3007, and L3009 being the best for more than four traits including seed yield and antioxidant compounds (Iannucci et al., 2021). Marker-aided backcrossing was employed to develop a set of barley near-isogenic lines (NILs) containing different combinations of *Ant1* (bHLH transcription factor) and *Ant2* (R2R3-MYB domain transcription factor) alleles (Gordeeva et al., 2019b). NILs carrying dominant alleles of both genes produced purple pericarp. The expression of these genes was upregulated in purple grain barley lines with dominant alleles at both loci. The lines carrying dominant allele either in the *Ant1* or the *Ant2* locus showed decreased level of expression of the dominant gene but scant activity of the recessive allele. Such an expression was barely detected in uncolored lines with recessive alleles at both loci. Marker-assisted selection approach to develop NIL containing phenolic compounds (anthocyanin and melanin) in the genetic background of barley cultivar "Bowman" was deployed which significantly showed higher total anthocyanin content without any yield-penalty (Glagoleva et al., 2022).

Substantial variation (47–1,289 μg g^{-1} dry weight) was observed in the anthocyanin seed content among wheat breeding lines (467–1,289 μg g^{-1} dry weight, mean = 881 μg g^{-1} in deep purple; 195–679 μg g^{-1}, mean = 496 μg g^{-1} in blue;

127–438 $\mu g\ g^{-1}$, mean = 221 $\mu g\ g^{-1}$ in purple) and cultivars (117–669 $\mu g\ g^{-1}$, mean = 354 $\mu g\ g^{-1}$ in blue and 47–175 $\mu g\ g^{-1}$, mean 100 $\mu g\ g^{-1}$ in purple). Deep purple lines contained higher concentration of anthocyanin followed by blue and purple lines. The analysis identified 10 target zones, four typically representing blue aleurone types, five purple pericarp types, and one representing both. The peak heights and areas were highly correlated and 7 of 10 target zones contributed to about 90% of the total variation. Multivariate analysis of seven target zones not only separated the lines into purple, blue and deep purple seeded types, but also identified lines with a specific anthocyanin pattern (Böhmdorfer et al., 2018).

A blue-grained substitution line in the genetic background of popular Russian wheat cultivar "Saratovskaya 29" (S29) including the *Thinopyrum ponticum* chromosome 4 has been developed (Gordeeva et al., 2019a). This substitution line contains 475.7 $\mu g\ g^{-1}$ anthocyanins compared to nil in S 29. Despite carrying the entire chromosome substitution, the 1,000-seed weight, milling, and dough characteristics were comparable or slightly lower than S29. Using genetic markers such as *Pp3* and *Pp-D1* (which regulate purple pericarp color) and morphological characteristics, the researchers developed a number of advanced bread wheat lines with multiple resistance to diseases and purple-seeded characteristics adapted to the West Siberian region and suitable for functional food production (Gordeeva et al., 2020). Colored grain wheat lines, with black ones having highest total anthocyanin content followed by blue, purple, and white have also been developed (Garg et al., 2016). The yield was similar to those of checks (amber wheat) in regional adaptation trials in India. The National Agri-Food Biotechnology Institute (NABI, Mohali) implemented a pilot project with support from the industry to develop three colored wheat cultivars, namely, "NABIMG-11-Black," "NABIMG-10-Purple," and "NABIMG-9-Blue" seed types (Garg, 2018a,b,c; **Figures 1**, **2**). The private sector entrepreneurs are involved through contract farming in the production, popularization, and marketing of processed colored wheat-based products in India. The black wheat cultivar "NABIMG-11-Black" has been gaining popularity among farmers, industry and consumers due to its potential health benefits as well as high-income generation potential. Its comparable yield (3.9 t ha^{-1}) and seed weight (43 g 1,000-seed) with control PBW621 (yield, 4.1 t ha^{-1}; 1000-seed weight, 38 g) after multi-season testing, showed the potential for significantly expanding its cultivation (NABI Annual Report, 2018–2019; https://nabi.res.in/cms?slug=annual-reports). Contract farming refers to agricultural production following an agreement between a buyer and farmer.

An anthocyanin-rich (deep purple pericarp) maize cultivar named "Polenta" (R3075) has also been developed (Lago et al., 2014). It ensued from recurrent selection (a method involving reselection generation after generation with interbreeding of selects to reshuffle genes through genetic recombination) in the genetic background of traditional cultivar "Scagliolo" devoid of anthocyanins in northern Italy. "Polenta" contains 109 mg 100 g^{-1} anthocyanins. The introduction of purple pigmentation in "Scagliolo" genetic background had adversely impacted 100-seed weight (0.198 vs. 0.254 g) and seed germination (84 vs. 92%). This colored "Polenta" cultivar is therefore an important genetic resource that can be recycled in maize breeding to develop lines combining high anthocyanins, acceptable seed size and seed germination to enhance its commercial value. The first anthocyanin-rich maize hybrid cultivar "Saekso 2" was released in South Korea (Choi et al., 2017). The average seed anthocyanin content in relation to "Saeko 1" (0 mg 100 g^{-1}) was 685 mg 100 g^{-1}. FlaNat Research Italia Srl (Italy) reported development of a new purple maize cultivar "Moradyn," which is adapted to northern Italy and maintains a highly pigmented cob (Ferron et al., 2020).

"Apache Red," a purple maize landrace, contains a wealth of diversity in anthocyanin composition and content. Using "Apache Red" and population breeding approach new populations were generated with variable flavonoid profiles–flavanol–anthocyanin condensed forms (0–80%), acylated anthocyanins (2–72%), pelargonidin-derived anthocyanins (5–99%), C-glycosyl flavone co-pigments up to 1,904 $\mu g\ g^{-1}$, and with anthocyanin content up to 1,598 $\mu g\ g^{-1}$(Chatham and Juvik, 2021). Thus, it represents to date one of the most anthocyanin diverse pericarp-pigmented source for use in maize breeding and genetics.

India is a home to several pigmented traditional landraces such as "Chak-hao Amubi," "Chak-hao Poireiton" and "Chak-hao Angangba," which are black-pigmented rice predominantly grown in Manipur. Pigmented rice cultivars, "Rubin" (red-grain) and "Yuzhnaya Noch" (black-grain), developed by crossbreeding are grown in Russia, while traditional landraces showing pigmented grains were collected in Philippines (Krishnan et al., 2020). Aromatic, black-grained rice lines have been developed through interspecific hybridization between *Oryza rufipogon*, a red grain donor and source of black rice gene *Kala4*, with cultivars "Badshabhog" (white grain), "Chenga" (red grain) and "Ranjit" (white grain) (Roy and Shil, 2021). A few nutrient-rich, black-grained rice cultivars namely "Pinhei 1," "Zhongi 4," and "Ziyunuo," which are increasingly popular with consumers, are cultivated in China; while a black rice introgression line in the genetic background of "Koshihikari" in Japan is nutritionally superior to the black-grained rice "Okunomurasaki" (Xia et al., 2021).

Clearly, significant progress has been achieved toward developing advanced breeding lines or cultivars with pigmented (black, purple, blue, or red) grains, with a few already commercialized such as barley, maize, rice, and wheat across continents. The produce from such cultivars may serve as potential sources for production of functional foods.

Transgenes and Gene Edited Crops

Genetic engineering of anthocyanin biosynthesis pathway in staple crops has the potential to provide health-promoting food in abundance to minimize the risk of chronic diseases in humans. However, anthocyanin biosynthesis pathway is complex and regulated by complex genetic network involving both structural and regulatory genes (**Table 3**) and influenced by agronomic practices and environmental factors (*Section Factors Affecting the Content and Composition of Anthocyanin*). Purple tomato rich in anthocyanins was developed by engineering two snapdragon

FIGURE 1 | Genetic variability for grain color [**(A)**, amber; **(B)**, purple; **(C)**, blue; **(D)**, black] in wheat.

FIGURE 2 | Advanced breeding lines with pigmented grains [**(A)**, amber; **(B)**, black; **(C)**, blue; **(D)**, purple] developed by crossbreeding and selection in wheat.

transcription factors (TFs) and it accumulated anthocyanins in fruits at levels substantially higher than previously reported and at concentrations comparable to the anthocyanin levels in berries (Butelli et al., 2008). The fruits showed intense purple color in both the peel and flesh and antioxidant capacity was increased three-fold. Tomato fruit produces large amounts of primary and secondary metabolites and therefore can serve as an excellent plant source to either increase nutrients for health-promoting biofortified foods or as a production system for high value new compounds (Li et al., 2018b). Also, tobacco cell cultures have been developed as customizable and sustainable alternatives to conventional anthocyanin production platforms by engineering regulatory and enzyme encoding genes, which were transferable to other plant species (Appelhagen et al., 2018).

A few research groups in field crops were successful in enhancing anthocyanins with little or no adverse effect on plant growth, development and reproduction (**Table 4**). A simple and an efficient multigene expression system based on embryo-specific bidirectional promotor and 2A linker peptides was developed for maize. Eleven genes were introduced into transgenic maize to rebuild the anthocyanin biosynthesis pathway in Hill embryos to develop anthocyanin-rich purple maize germplasm (Liu et al., 2018a,b). A highly efficient vector system for transgene stacking involving a construct containing eight anthocyanin-related genes driven by the endosperm-specific promoters, a selectable marker and a gene for marker excision was successful in generating a novel "purple endosperm" rice germplasm with high anthocyanins (Zhu et al., 2017). It involved expression of the transgenes that enhanced the expression of 13 endogenous anthocyanin biosynthesis genes. Both the approaches provided an efficient and a versatile toolkit for transgene stacking to increase synthesis of anthocyanins.

Genes *ZmC1* and *ZmR* control anthocyanin biosynthesis in maize. Transgenic wheat lines overexpressing *ZmC1* and *ZmR* had highest pigmentation in almost all tissues including seeds, while those overexpressing *ZmC1* or *ZmR*, respectively, had controlled pigmentation in vegetative or reproductive tissues including seeds. The transgenic lines showed greater expression levels of transcripts, conserved homologs, and six wheat structural genes associated with anthocyanin biosynthesis (Riaz et al., 2019). The overexpression of *ThMYC4E* in transgenic bread wheat showed higher levels of anthocyanins, predominantly cyanidin and delphinidin in seeds, and which had little or no adverse impact on plant growth and development (Zhao et al., 2020). Thus, agronomically valuable anthocyanin-rich genetic resources for crossbreeding are available.

Red seeded rice is a rich source of proanthocyanidins and anthocyanins. Two complementary genes *Rc* and *Rd* control red color. A 14-bp frame-shift deletion in the seventh exon of the *Rc* in cultivated rice resulted in white grains (Sweeney et al., 2007). CRISPR/Cas9 system was deployed to functionally restore *rc* allele by reverting the 14-bp frame-shift deletion to in-frame mutations, and successfully converted elite white pericarp rice cultivars into red seeded types, which led to a significant increase in proanthocyanidins and anthocyanins agronomically at par with WT (Zhu et al., 2019). CRISPR/Cas9 gene editing system is promising to convert white-seeded into red-seeded rice cultivars. Multinational seed private enterprises are racing to develop CRISPR-edited crops with agriculturally beneficial traits. However, there are many hurdles, including regulation, public acceptance, social and ethical concerns, and whether such crops are going to be categorized as GMOs or non-GMOs. CRISPR-edited crops should be more socially acceptable since such crops are not based on transgenes (Ahmad et al., 2021).

Model Food to Assess Diet-Health Complexity

Ascertaining the beneficial effect of anthocyanin-rich food is limited, due to confounding effects by the influence of other metabolites in plant-based food consumed in the diet. Maize is an important food and feed crop with multiple and diverse sources of germplasm with colored grains, and well-researched flavonoid biosynthetic pathway which make it an ideal crop for the development of "near-isogenic" model foods differing only in the content of specific classes of flavonoids, which can be used in animal feeding/human intervention trials to unravel diet-health complexity (Petroni et al., 2014). NILs either lacking both "anthocyanins" and "phlobaphenes," containing either "phlobaphenes" or "anthocyanins," and a line that contains both "anthocyanins" and "phlobaphenes" are available. The profiling of these NILs and comparing them to those lacking one or both compounds revealed that "anthocyanin" and "phlobaphene" accumulation contributed significantly ($P < 0.05$) to antioxidant capacity, while intake of flavonoid-rich maize diets ameliorated experimental colitis in mice. It is a powerful tool to investigate the disease-preventive effects of specific flavonoid compounds in diet (Wu et al., 2021a). Tomato, a widely consumed vegetable worldwide, has abundant genetic and genomic resources. The fruits contain a variety of essential nutrients (minerals, vitamins, proteins, essential amino acids, monounsaturated fatty acids, carotenoids, phytosterols) and antioxidant-rich phytochemicals beneficial to human health (Ali et al., 2021). The variation in color, shape, texture, and volatile compounds make it a unique model organism of *Solanaceae* family. The growing evidence supports the connection between increased tomato consumption and reduced risk for cardiovascular disease, cancer, neurodegenerative diseases and diabetes, maintenance of a healthy gut microbiome, and improved skin health, fertility, immune response, and exercise recovery (Canene-Adams et al., 2005; Collins et al., 2022). The antioxidant capacity of the genetically engineered tomato fruit containing two snapdragon TFs increased by three-folds and prolonged the life of cancer susceptible mice (Trp53$^{-/-}$) raised on a diet supplemented with the high-anthocyanin tomatoes (Butelli et al., 2008). Inflammatory bowel diseases (IBD) are chronic inflammatory disorders because of defective immune response toward intestinal bacteria. Intestinal dysbiosis is associated with the onset of IBD that persist even in patients in deep remission. A dietary regime enriched in polyphenols, tomato NILs in the genetic background of Bronze-tomato enriched in flavonols, anthocyanins, and stilbenoids (Scarano et al., 2018), administered to Winnie and control mice showed significant induction of anti-inflammatory genes and may efficiently support IBD remission affecting the intestinal dysbiosis (Liso et al., 2018). Both crossbreeding and biotechnology approaches were used to develop anthocyanins rich germplasm/cultivars (Mattoo et al., 2021), which may be further crossed to develop NILs differing in a particular biochemical compound to investigate its long-term effect on human health. The transcription factors involved in regulating the structural and other genes in the biosynthetic pathway of anthocyanin are depicted in **Figure 3** (Courtesy of Frontiers—image_m/fchem-06-00052-g005.jpg).

SENSIBILITY AND ACCEPTABILITY OF ANTHOCYANIN-ENHANCED FOOD PRODUCTS IN RELEVENCE TO HUMAN HEALTH

Food Products Prepared From Grains Developed by Crossbreeding

Insufficient global intake of minerals, vitamins, fibers and phytochemicals, particularly among the poorer communities, is the main cause of malnutrition. HarvestPlus under CGIAR-Research Program on Agriculture for Nutrition and Health (https://a4nh.cgiar.org/) has provided the platform and one time investment to implement cost-effective crop biofortification as key intervention to reduce mineral and vitamin deficiencies in the developing world. Biofortification refers to the development of micronutrient-dense staple crops using traditional breeding practices or biotechnology. Biofortified crops have been released in 40 countries, with more than 48 million people in small holder family benefitting from nutrient dense (Fe, Zn, β-carotene) cultivars (https://www.harvestplus.org). Such crops offer a rural-based intervention by the farmers. Assessment of adoption and consumption of biofortified crops suggest high preference of nutritionally enhanced crops by the target consumers (Dwivedi et al., 2012; Birol et al., 2015). Integrating anthocyanin to biofortification will provide a platform for developing nutrient (Fe, Zn, β-carotene) and anthocyanin-rich staple crop cultivars. The mainstreaming biofortified traits into public and private sector breeding programs, building consumer demand, and providing appropriate policy support is needed to scale up production and consumption of nutrients and/or phytochemicals-rich staple foods together with helping the poorer sectors (Bouis and Saltzman, 2017; Foley et al., 2021).

The demand for anthocyanin-rich food is anticipated to increase with time because of the health benefits. Cultivar development is a time-consuming process, for example, from the time a cross is made to the advancement, testing and release of a new cultivar, it takes 8 to 10 years, and then at least another 5–8 years to upscale production and popularization of new product among all stakeholders. Targeted breeding has led to the development and cultivation of anthocyanin-rich crops (**Table 4**) though on a limited acreage. Replacing the non-pigmented grains on large acreage to pigmented grains is not easily achievable. An incremental increase in acreage and addressing bottlenecks to production and acceptance of biofortified food-products and policy support by Governments may provide stimulus for large-scale adoption and consumption of biofortified crop produce by agrarian society. A paradigm shift is therefore needed to include nutrition and other health promoting compounds as core breeding issues such as resistance to pest and diseases and productivity. In comparison, transgenics approach on the other hand requires much shorter time frame in which a multi-nutrient product can be developed using a single DNA insertion, as evidenced in rice expressing *AtNAS1*, *PvFERRITIN*, *CRTI*,

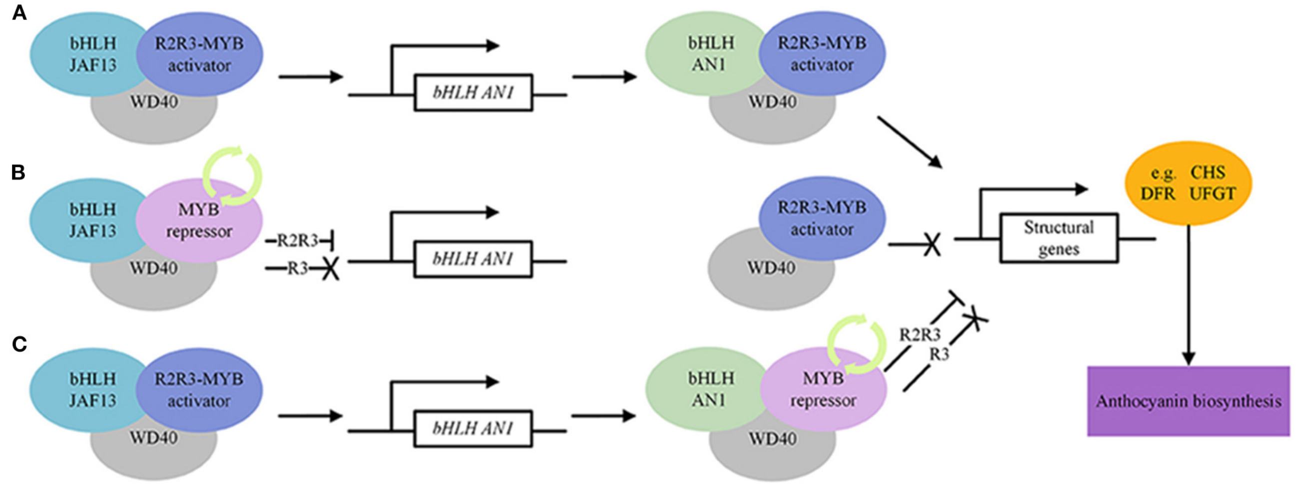

FIGURE 3 | Regulatory transcription factors in anthocyanin biosynthesis pathway. MYB, bHLH and WD40 modulate the expression of structural genes. **(A)** Activate regulation of anthocyanin biosynthesis. **(B)** Repressive regulation of anthocyanin biosynthesis. MYB repressors compete with MYB activators for bHLH JAF13. **(C)** Repressive regulation of anthocyanin biosynthesis. MYB repressors compete with MYB activators for bHLH AN1. The "→ " means activation, "—|" means repression and "X" means inactivation. https://www.frontiersin.org/files/Articles/308869/fchem-06-00052-HTML/image_m/fchem-06-00052-g005.jpg.

and *ZmPSY* genes in polished grains enriched with Fe, Zn, and β-carotene (Singh et al., 2017).

Biofortification may result in altering sensory and flavor attributes, appearance, and other characteristics of food. The anthocyanin-rich food products, including grains and their derived flours, bread, noodles, tortilla, biscuits, and other confectionary products are often seen in grocery stores or supermarkets worldwide (Betran et al., 2001; Syed Jaafar et al., 2013; Urias-Peraldí et al., 2013; Havrlentova et al., 2014). The public perception about acceptance of anthocyanin-rich food will also depend on the availability, affordability, and willingness to pay higher price for nutritionally-enhanced foods vis-à-vis commonly derived products involving white grains and flours.

A significant proportion of wheat is consumed in the form of "chapatti" or flat bread. The research suggests that "chapattis" made from anthocyanin-biofortified wheat flour have soft texture, acceptable sensory quality, good taste, are rich in dietary fibers and protein, but are low in carbohydrates (Kumari et al., 2020). A higher total amino acid content and nutrition index in black and blue wheat flour and chapatti in comparison to other (amber, or purple) flour and chapatti samples has been noted (Sharma et al., 2022). The essential amino acids, however, were similar in flour and chapatti samples. The amino acids on an average were reduced by 11.41, 12.4, 19.0, and 23.8% in black, blue, purple, and white wheat, respectively. The white chapatti samples showed >20% loss in 14 amino acids, while such reduction in black chapatti was noted for only one amino acid. Higher retention of amino acids in colored wheat could be due to the masking and protective effects of anthocyanins on proteins and amino acids from heating and oxidative damage.

A study on bread-making quality and organoleptic properties of bakery products made from anthocyanin-rich wheat showed no difference (rather in some cases higher) than the corresponding properties of products made from colorless wheat grains. A variety of products including bars, crackers, bread, pancake, and porridge made from purple wheat flour substantially differ in nutrition, protein being high in bread, pancake, and porridge and intermediate in bars and crackers. The bran-rich products and whole wheat pancake are rich in dietary fiber. The crackers and bars have higher anthocyanin and dietary fiber with strong antioxidant capacity (Gamel et al., 2020). The anthocyanin-based bakery products increase shelf life and resistance to molding under conditions that are favorable to fungal infection (Khlestkina et al., 2017). Nutritional significance of confectionery products made from flour and bran fraction of anthocyanin-rich (purple) or anthocyanin-poor (white) wheat isogenic lines have been compared (Usenko et al., 2018). The products made from purple-seeded wheat isogenic line had ∼2.5-fold higher anthocyanins than in the similar products obtained from white-seeded isogenic line. Thus, use of purple wheat bran as ingredient-enriched confectionery products with a high nutritional value has immense possibilities. However, as noticed with maize in India (Trehan et al., 2018) and wheat in Italy (Pasqualone et al., 2015), people preferred muffins prepared using yellow maize than those made with purple corn, or biscuits from non-pigmented wheat rather than those derived from anthocyanin-rich purple wheat, respectively. It is also known that the different appearance and flavor negatively affect the view on an anthocyan-derived food product (Hegyi et al., 2016), while the perceived health benefits increase their acceptance (Lampila et al., 2009).

Polvorones, a traditional flour-based confectionery made with whole blue maize flour has higher content of phenolics and anthocyanins as well as antioxidant activity compared with wheat flour-based confectionery. Substitution of wheat flour with whole blue maize flour thus enhanced overall acceptability, as well as the color and flavor of polvorones (Vázquez-Carrillo et al., 2018). There is growing demand for native-traditional foods to improve their intake of both nutrients and health-promoting phytochemicals. A comparative assessment of nutrients and bioactive compounds between industrial and handmade tortillas revealed that handmade tortillas made from blue and white maize were superior in nutritional and bioactive compounds compared to industrial tortillas. The handmade blue maize tortillas showed greater dietary fiber, phenolic acids and anthocyanins and antioxidant capacity than white maize-based industrial tortillas. The ferulic acid in handmade blue tortillas was 4.5-fold greater compared to industrial white maize tortillas. Thus, handmade fresh tortillas are superior in nutritional-nutraceutical properties compared to white maize tortillas (Colín Chávez et al., 2020).

Popcorn is an extremely popular snack globally. No difference was found in popping ability and expansion volume as well as taste perception between popcorn obtained from purple (∼66 mg 100 g^{-1} dry matter, mainly cyanidin) or colorless (yellow kernels) cultivars (Lago et al., 2012). Even though the microwave-assisted popping reduced anthocyanin content by ∼46%, the remaining anthocyanin provided a strong antioxidant capacity compared to the colorless grains. The demand for blue maize products in Mexico is booming and consumers are willing to pay a premium price (women, up to 33%; men, up to 19%) for its rich flavor and texture. The desire to go back to natural and to their roots drive consumers to pay higher price for blue maize products (https://www.cimmyt.org/news/blue-maize-is-all-the-rage-but-are-consumers-willing-to-pay/).

Thus, there is a growing awareness among people at large to eat nutritious and health- promoting foods. The availability, affordability and public perception about the unconventional foods that differ in appearance, sensory and flavor attributes limit the intake of such products. However, public perception is gradually changing to favor such foods for health reasons (Talsma et al., 2017; Woods et al., 2020; Rizwan et al., 2021), as also evidenced by the stockpiling of bakery and confectionary products made from colored grains or flours in grocery stores and supermarkets worldwide. The intake of such products is expected to rise many fold once such crops are commercialized for production in the countryside.

Genetically Engineered Anthocyanin-Enhanced Crop-Based Food Products

Public reluctance about the acceptance of foods derived from grains or flour of transgenic or gene edited crops, relative to foods produced using crossbreeding, is largely due to wrong perception of unknown consequences of adverse effect on human health of the former. Heterogeneity of consumers across cultures of borders, attitude toward science and innovations, and in risk perceptions emerge as key determinants for acceptance and willingness to pay (WTP) for genetically modified food (GMF). Acceptance and WTP are higher when consumers perceive the attributes (nutritional value, taste and flavor or sustainable ecosystems such as reduced water or pesticides) generated by new technology are beneficial. The gene edited-derived foods are systematically less discounted than GMF (Beghin and Gustafson, 2021). Vitamin A deficiency is a public health problem in developing world prompting country-Governments to adopt biofortification of plant-derived foods with pro-vitamin A (β-carotene) enriched foods as vehicle to overcome deficiency. Cassava, maize and sweet potato have been successfully biofortified by exploiting natural genetic variation with elevated levels of provitamin A (Welsch et al., 2010; Nkhata et al., 2020). Rice grains are devoid of β-carotene. The accumulation of β-carotene in the endosperm, popularly coined as "Golden Rice," was successfully achieved by introducing *Zmpsy1* and *crtI* into a US temperate *japonica* rice, Kaybonnet (Ye et al., 2000; Paine et al., 2005). This golden trait was subsequently transferred by marker-aided backcross breeding into several locally adapted cultivars (IR64, PSBRc82, BR29) in Asia (Mallikarjuna Swamy et al., 2021). More importantly, no significant differences in seed chemistry, except for β-carotene and related carotenoids, between genetically engineered GR2E ("Golden Rice") and the near isogenic control were noted. The efficacy trials revealed that milled rice of GR2E could contribute up to 89–113% and 57–99% of the estimated average requirement for vitamin A for preschool children in Bangladesh and the Philippines, respectively (Mallikarjuna Swamy et al., 2019). Both Bangladesh and the Philippines have taken the lead in providing their constituents, respectively, Bt brinjal (eggplant) and GMO maize which have transformed their farmers (Shelton et al., 2018; https://allianceforscience.cornell.edu/blog/2019/01/gmo-corn-transforming-farmers-lives-philippines/). More recently, Department of Agriculture-Philippine Rice Research Institute (DA-PhilRice) in partnership with the International Rice Research Institute (IRRI) has recommended release of provitamin A rich (β-carotene) golden rice cultivar in the Philippine (https://www.irri.org/news-and-events/news/philippines-becomes-first-country-approve-nutrient-enriched-golden-rice).

Furthermore, molecular characterization and biosafety assessment has revealed that biofortified provitamin A rice is safe to eat without any adverse impact on human health (Oliva et al., 2020). "DA-PhilRice" in the genetic background of PSBRc82 has been recently released for commercialization in the Philippines. "DA-PhilRice" has also received food safety approvals from regulators in Australia, New Zealand, Canada, and USA, and is likely to be released soon in Bangladesh. The evidence suggests that consumers have reacted positively to "Golden Rice" and thus can be utilized for food systems to be integrated into consumer diets. In near future, new products enriched with nutrients and bioactive compounds (including anthocyanin), irrespective whether developed by conventional crossbreeding or by use of genetic engineering (including gene editing), are likely to be released for commercialization and will likely be accepted by public in large as staple foods in the developing world to promote human health (Steur et al., 2022).

CONCLUDING REMARKS

Secondary metabolism in plants is a source of many potential bioactive compounds some of which have been linked to human health. Anthocyanins belong to a major group of polyphenolic molecules called flavonoids. The biosynthetic pathways leading to synthesis of these bioactive compounds are regulated by a complex of structural and regulatory genes as well as environmental cues. Thus, anthocyanin biofortification is providing new knowledge and advancements in gene stacking through core breeding programs and metabolic engineering advancements to ensure future rich germplasm for nutrition needs of growing human population particularly in the developing world. Both core breeding and genetic engineering of transcription factors have been successfully applied in developing anthocyanin-rich germplasm without significant yield penalty. The evidence suggests that there are changes in public perceptions about the acceptance of biofortified food crops, whether developed by crossbreeding, genetic engineering or gene-editing. The crops include Fe, Zn, or β-carotene dense beans, corn, rice, and wheat developed by crossbreeding; β-carotene enhanced "Golden Rice" by genetic engineering. This certainly is a good avenue for improving the human health worldwide. Thus, including phytochemicals as additional quality parameter for developing nutrients and phytochemicals dense staple crop cultivars and promoting large-scale production and intake of such food products should be the guiding principles to minimize the risk of all forms of malnutrition in human globally. Technological challenges to anthocyanin research include a rapid and cost-effective phenotyping assay capable of analyzing large number of breeding samples, anthocyanin retention and bioavailability, and loss of anthocyanins during cooking/baking or during storage. Confounding effects of food matrix in determining the health benefits associated with phytochemicals is equally challenging to be performed on human. Such issues should be addressed by education and transparency of the methodologies employed to achieve these goals for human health worldwide. Moreover, adopting a science-based regulatory frame uniformly worldwide as well as public awareness is seen as a good knowledge base to promote human consumption of transgenic and gene edited staple crops (Kato-Nitta et al., 2019, 2021; Wu et al., 2021b).

AUTHOR CONTRIBUTIONS

SD and AM: conceptualization, investigation, writing-original draft, and writing-review and editing. MG, SD, and BS: investigation and writing-original draft. RO: conceptualization, project administration, investigation, writing-original draft, and review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsufs.2022.867897/full#supplementary-material

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