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Review

Breeding Low-Cadmium Wheat: Progress and Perspectives

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Abstract: Farmland cadmium (Cd) contamination has adverse impacts on both wheat grain yield and people's well-being through food consumption. Safe farming using low-Cd cultivars has been proposed as a promising approach to address the farmland Cd pollution problem. To date, several dozen low-Cd wheat cultivars have been screened worldwide based on a Cd inhibition test, representing candidates for wheat Cd minimization. Unfortunately, the breeding of low-Cd wheat cultivars with desired traits or enhanced Cd exclusion has not been extensively explored. Moreover, the wheat Cd inhibition test for variety screening and conventional breeding is expensive and time-consuming. As an alternative, low-Cd wheat cultivars that were developed with molecular genetics and breeding approaches can be promising, typically by the association of marker-assisted selection (MAS) with conventional breeding practices. In this review, we provide a synthetics view of the background and knowledge basis for the breeding of low-Cd wheat cultivars.

Keywords: cadmium; farmland; wheat; cadmium resistance; breeding methods

1. Introduction

Cadmium (Cd), being a non-essential element, is among the most toxic metals [1]. Cd and Cd-bearing minerals have been widely used in modern industries and agriculture. Globally, metal industries produce 24,000 tons of Cd each year, with China being the top producer [1]. Meanwhile, worldwide, 17.5 Tg of Cd-bearing phosphate fertilizers are applied annually in recent years, about 50% of which are applied in China, the United States (US), and India [2]. Surveys showed that European phosphate fertilizers contain 7.4 mg/kg Cd on average [3], which is around 20-fold higher than the Cd geological background. Phosphate fertilizers that are produced in the US contain considerable amounts of Cd as well (4–109 mg/kg) [4]. Globally, the increasing use of phosphate fertilizers since the 1960s has inevitably caused widespread farmland Cd pollution. Wastewater irrigation and dry deposition have also created hotspots of Cd-polluted land [5]. As a result, farmland Cd pollution has been a major concern for decades in many industrialized and developing countries. For example, about 9.5% of Japanese paddy soil is more or less polluted by Cd. In China, official reports showed that 7% of China's farmland is Cd-contaminated.

Farmland Cd pollution poses considerable risks to human health through the consumption of foods with excess Cd, particularly staple foods. Wheat (*Triticum aestivum* L.) is a staple food crop for nearly 35% of the world population [6]. Since 1991, China has been one of the top wheat producers in the world. In the year 2016, China produced 128 million metric tons of wheat on its 24 million hectares of farmland. Nonetheless, wheat Cd contamination has inevitably been a hot topic in China as a result of farmland pollution. In Dakuai Town of Xinxiang, Henan, China, at least 150,000 kg of wheat with Cd levels 1.7–12.8-fold higher than the national food standards is produced each year. More "Cd wheat" can be found in the vicinity of many industrial gathering areas in Xinxiang. In 2016, about 666 ha of wheat field in the Muye District of Xinxiang was changed to a plantation of garden plants and flowers due to heavy metal contamination. Moreover, "Cd wheat" has also been detected in some wastewater irrigation areas of Shijiazhuang [7], Kaifeng [8], Beijing [9], and Tianjin [10]. The identified, as well as more unidentified, wheat Cd contamination has posed a considerable health risk to people, particularly the local people. Long-term exposure to Cd, even at a low rate, will cause bone diseases, emphysema, and proteinuri [11]. Therefore, minimizing food heavy metal pollution, including wheat Cd contamination, is now a priority task in the “Prevention and Control of Soil Pollution Action Plan” released by the Chinese government on 28 May 2016.

Safe farming of the polluted farmland, which aims to produce metal-safe crops without purposefully removing soil heavy metals, is thought to be one of the best strategies. Safe farming in Cd-polluted farmland has involved several biomaterials and agronomic measures, and low-Cd cultivars are recognized as an economic and sustainable one. Low-Cd wheat cultivars are supposed to be effective and essential in the polluted farmland of wheat–maize rotation areas, typically in the Yellow River and Huai River Valleys of China. The screening of low-Cd cultivars was started decades ago [12], though it was not proposed as a formal measure for heavy metal pollution control until 2006 [13]. Since then, many studies have been purposefully dedicated to the screening of low-Cd cultivars, most of which are wheat and rice cultivars. There have also been several excellent reviews on the selection of low-Cd (Cd-safe) cultivars [14,15]. In this review, we focus on the exploration of possible schemes of low-Cd cultivars breeding, based on a synthetic view of the phenotypic and genotypic responses of wheat to Cd and the available breeding strategies.

2. Cd Effects on Wheat Growth and Development

In general, the presence of more than 5–10 mg/kg of Cd in agricultural soil has adverse effects on crop cultivations [16]. The Cd toxicity symptoms that were observed in crops may arise due to the wide range of interactions at the cellular level. A huge number of studies have reported the impacts of excess Cd uptake on crops metabolism and physiological processes [17–22].

In wheat, Cd stress has induced several biochemical disorders of the cell membrane, lipid and protein synthesis, and nutrient metabolism, as well as decreases in the chlorophyll content [23–25]. Wheat exposed to high levels of Cd shows visible symptoms of chlorosis, necrosis, spotting of roots, and a reduction in leaf number and leaf area [26,27]. In wheat, root epidermis is the primary acting site of Cd toxicity, where roots significantly accumulate more Cd than other plant parts [28,29]. Cd had intensive effects on root growth and elongation, normally decreasing the root/top ratio. Cd induces several oxidative signals at root membrane sites that elicit programmed cell death (PCD). Wheat photosynthetic pigments are also sensitive to Cd stress, especially the structure and function of chloroplasts [30].

Soil Cd contamination has a substantial impact on the quantitative traits of wheat plants. Rebekic and Loncaric [31] evaluated 51 winter wheat cultivars under 20 mg Cd kg^{-1} soil for yield and yield-related traits. Their results showed that high soil Cd concentrations caused a significant reduction in wheat seed weight per spike by 27%, followed by reductions in kernel weight and seed number per spike by 5.2% and 23%, respectively. Similarly, Ci and his colleagues (2009) evaluated four wheat cultivars under 0.050 M of Cd concentration for morphological characteristics. They found a visible decrement in most of the growth and root parameters under Cd toxicity [32]. In roots, Cd competes for absorption with other mineral nutrients sharing similar chemical properties with Cd, such as Ca^{2+} and Mg^{2+}, causing a mineral deficiency in plants. The available evidence showed that Cd treatment reduced the amount of nitrate salts and sugar concentrations, while it amplified the free amino acid concentrations in wheat roots and shoots [32,33].

3. Molecular Mechanisms of Cd Resistance in Wheat

Unlike rice, wheat (a hexaploid) has not been extensively explored regarding its genetic determinants for Cd tolerance. In this section, we reviewed the identified genes and molecules that are involved in wheat antioxidation processes, metal sequestration, exclusion, signaling pathways, and transcriptional regulation (Figure 1).

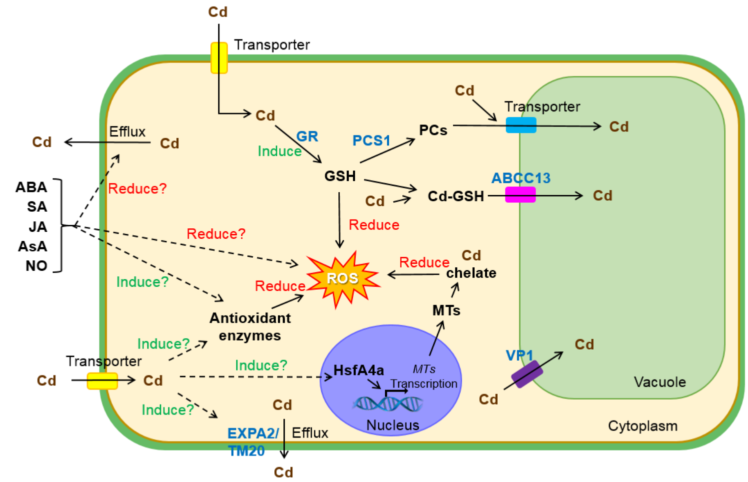

Figure 1. A diagram explaining the molecular mechanisms of cadmium (Cd) resistance in wheat. ABA, abscisic acid; SA, salicylic acid; JA, jasmonic acid; AsA, ascorbic acid; NO, nitric oxide. ROS, reactive oxygen species; GR, glutathione reductase; GSH, reduced glutathione; PCs, phytochelatins; PCS1, PC synthase 1; MTs, metallothioneins. ABCC13, ATP binding cassette subfamily C member 13.

3.1. Antioxidation and Sequestration

Cd can inhibit the antioxidant defense system of plants and induce the formation of reactive oxygen species (ROS), which could cause oxidative stress [34–36]. As a conservation strategy, plants accumulate a variety of antioxidant products, such as reduced glutathiones (GSHs), to protect functional proteins from oxidative damages. In wheat, chronic Cd exposure increased the activity of glutathione reductase (GR), a key enzyme maintaining the content of GSH [37]. Induction of distinctive isoforms of GR has been observed in wheat, indicating a GR-associated defense mechanism against Cd stress [37].

Heavy metal-GSH conjugates can be transported into vacuoles by ABCC (ATP binding cassette subfamily C) transporters [38–40]. Heterologous expression of *TaABCC13* conferred tolerance to heavy metals by the utilization of GSH, which was in accordance with the fact that the silencing of *TaABCC13* leads to sensitivity to Cd in transgenic wheat [41]. *TaABCC13*, also called *TaMRP3*, enhanced the Cd tolerance of yeast *ycf1* mutant through the GSH-mediated detoxification pathway [42,43]. GSH is also the precursor of many phytochelatins (PCs), synthesized by PC synthase (PCS) [44,45].

Heavy-metal-complexing PCs could decrease Cd content in eukaryotic cells by Cd sequestration and thus ameliorate Cd-induced oxidative stress [46,47]. *Arabidopsis* alcohol dehydrogenase (*Adh*) promoter-driven *TaPCS1* expression caused a specific root expression of TaPCS1 in *cad1-3* (an *AtPCS1* loss-of-function mutant) [48]. Adh::TaPCS1/*cad1-3* complemented the Cd sensitivities of the *cad1-3* and showed induced Cd^{2+} and PC content in *Arabidopsis* shoots [48], indicating an enhanced Cd tolerance function. However, contradictory results were also observed when PCS was overexpressed in *Arabidopsis* and tobacco [49–51]. Wang et al. [52] reported that the heteroexpression of *TaPCS1* in rice reduced Cd tolerance and increased Cd accumulation and PC content in shoots. GSH reduction might result in Cd sensitivity, yet more evidence is required to clarify the function of a single PCS gene in response to Cd stress.

Another reported sequestration-related protein in wheat is TaVP1, a vacuolar H^+-pyrophosphatase (V-H-PPase). *TaVP1* was first cloned by Brini et al. [53], and its function in Cd tolerance was evaluated by being ectopically expressed into tobacco [54]. The transgenic lines showed enhanced Cd tolerance, higher Cd accumulation, and higher CAT activity when compared with the wild type [54].

3.2. Exclusion

The ability to preclude or reduce root Cd uptake is a key resistance mechanism in plants. To date, little is known about Cd exclusion-related genes in wheat. Kim et al. [55] reported a wheat transmembrane protein, encoded by *TaTM20*, which conferred Cd tolerance when expressed in yeast cells. The expression of *TaTM20* induced Cd efflux, which caused lower Cd content in yeast cells, even under the condition of reduced GSH content.

3.3. Phytohormone and Signal Molecule Regulation

A number of studies showed that plant hormones and signal molecules were involved in plant Cd response, such as salicylic acid (SA), abscisic acid (ABA), jasmonic acid (JA), ascorbic acid (AsA), and nitric oxide (NO) [56]. Exogenous AsA treatment significantly increased NO and endogenous AsA contents, inhibited ROS accumulation and Cd absorption, and enhanced the Cd tolerance of wheat seedlings [57]. NO is a well-known secondary messenger that regulates plant response to abiotic stress. Evidence was also shown that exogenous NO induced Cd resistance in wheat seedlings [57]. Similarly, results have also indicated the protective role of exogenous SA against Cd stress in maize and barley [58,59]. Kovács et al. reported that Cd induced SA synthesis in wheat, and wheat genotypes with different levels of tolerance exhibited various SA contents in accordance with GSH metabolism, indicating a role of SA-related signaling in Cd tolerance in wheat [60].

3.4. Transcriptional Regulation

Transcriptional factors (TFs) play important roles in regulating Cd detoxification-related genes in plants. A number of studies demonstrated that some Cd response TFs, such as AtbHLH29/38/39 [61], BnbZIP2 [62], ZAT6 [63], and PvERF15 [64], enhanced plant Cd tolerance transcriptionally. Shim et al. reported that TaHsfA4a, a class a4 heat shock transcription factor from wheat, conferred Cd resistance in both yeast and rice [65]. The knockdown of OsHsfA4a, which is a homolog of TaHsfA4a, decreased Cd resistance in transgenic rice [65]. Further functional analysis showed that the DNA binding domain (DBD) of TaHsfA4a was crucial for Cd tolerance. Moreover, *TaHsfA4a*-mediated Cd tolerance in yeast cells was found to be metallothionein (MT) gene-dependent, suggesting that *TaHsfA4a* might confer Cd tolerance by upregulating the expression of MTs in wheat [65].

3.5. Other Mechanisms

Recently, Dobrikova et al. [66] reported a wheat *Rht-B1c* mutant that showed enhanced Cd tolerance under 100 μM Cd treatment. The mutant expressing aberrant DELLA proteins showed limited gibberellic acid (GA) responsiveness, which caused growth repression [67].

Ren et al. reported a wheat expansin gene, *TaEXPA2*, which was upregulated in leaves when subjected to Cd stress [68]. Expansins are cell wall-located proteins that regulate plant development and response to various abiotic stresses [69–72]. Under Cd stress, *TaEXPA2* conferred improved germination rate, root elongation, biomass accumulation, and photosynthesis when overexpressed in tobacco. The transgenic lines exhibited an efficient efflux of Cd, lower Cd accumulation, and enhanced antioxidant enzyme activities in comparison with the wild type [68]. These results suggested that *TaEXPA2* may regulate plant Cd tolerance, probably through the activation of Cd efflux and antioxidation.

P_{1B}-ATPases, also called heavy metal ATPases (HMAs), play direct roles in plant heavy metal transmembrane transport. Tan et al. reported that *TaHMA2* was involved in the long-distance transport of Zn/Cd in transgenic rice [73]. *TaHMA2* conferred transgenic yeast cells a better Cd tolerance. The overexpression of *TaHMA2* in rice increased the root-to-shoot transport of Cd, and the transgenic rice showed better Cd resistance under low Cd treatment [73].

4. Breeding Strategies for Low-Cd Wheat Cultivars

Low-Cd wheat cultivars are the most effective, viable, and economic mean to reduce Cd health risks that are related to food consumption. Enhancement of wheat Cd-stress and reduction in grain Cd uptake can be realized by both conventional and modern breeding methods. In conventional breeding, low-Cd wheat cultivars are selected based on the measurements of morphological, physiological, or biochemical parameters that are associated with Cd stress. To improve the genetic background of wheat cultivars with enhanced Cd resistance, intra-specific crosses among superior individuals are usually developed, followed by selection in succeeding generations. To handle segregating materials, breeding methods, such as mass selection, pure line, and recurrent selection methods can be effectively used in the development of low-Cd wheat cultivars. However, the tolerance established in crops with conventional methods is usually not very robust or broad-spectrum [74]. Conventional selections are dependent upon several environmental variations and thus require a widespread location/generation field trial, delaying the progress of cultivar development [75]. As a general breeding criterion, 8–10 years of substantial breeding efforts are required to breed a cultivar right from the pre-breeding phase up to commercial release [76]. Modern breeding practices that create genetic difference along with enhancements in screening and selection compensate to a large extent for conventional breeding.

The recent advancements in molecular genetics knowledge have established many modern breeding methods to confer Cd resistance in wheat. Progress in wheat against Cd stress continues by exploiting molecular breeding tools, such as marker-assisted selection, allele discovery, allele pyramiding, genome mutation, association mapping, genome selection, and next-generation sequencing [77]. Currently, there are two key molecular approaches to assess Cd stress in wheat: marker-assisted selection and genomic selection [78]. Molecular markers have been widely used in bi-parental mapping and genome-wide association (GWA) studies to underline and characterize candidate genes and favorable alleles that are associated with Cd stress in wheat [79]. On the functional basis, the associated markers have a breeding value that is based on the association of phenotype and marker genotype. The summation of all breeding values has potential impact in the selection process of low-Cd cultivars. Yet, as these breeding methods are becoming progressively fast and accurate, plant breeders favor them for decreasing the environmental pressure on breeder selections. The adoption of molecular breeding methods and their successful integration with conventional breeding methods will have potential impact on the development of low-Cd wheat germplasm.

4.1. Genetic Variation and Selection of Low-Cd Wheat Cultivars—Conventional Breeding Approaches

Conventional breeding has been successfully utilized and considerable breeding progresses/genetic gain has been achieved in many traits, such as yield, quality, and stress ability. Practicing conventional methods for adaptation to abiotic stresses is challenging, as compared to breeding for other plant characters. For each of the abiotic stresses there are different mechanisms of resistance, which can be contrary, depending on the plant stress-adaptive nature [80]. However, conventional breeding methods have certain limitations and drawbacks, and thus little achievement has been gained so far in the breeding of wheat for abiotic stresses, especially Cd stress. Plant breeders generally practice conventional breeding methods, i.e., introduction, selection, and hybridization in favor of the development of low-Cd wheat cultivars. As a result, several low-Cd wheat cultivars were imperatively developed through conventional breeding approaches. For example, Yue et al. (2018) evaluated three wheat cultivars—Sumai 3, Jingdong 8 (JD 8), and Nannong 9918—under four different Cd levels [81]. Their results listed JD 8 as a Cd-tolerant cultivate, containing the lowest Cd content and relatively less toxicity as compared to Sumai 3 and Nannong 9918 cultivars. Similarly, 15 wheat cultivars were tested under Cd concentrations of 15, 30, and 45 μM. The results revealed that Lasani-2008 and Iqbal-2000 exhibited the lowest Cd contents, while Sehar-2006 and Inqlab-91 exhibited the highest Cd concentration in shoots [82]. Moreover, a large number of conventional studies were performed to screen out Cd-safe wheat cultivars (Table 1).

Breeding for the low-Cd trait requires reliable knowledge of natural variation among the given population, pedigree information of cultivars, and future breeding strategies for developing and pyramiding low-Cd traits with other quantitative traits [14]. Wheat species and cultivars vary extensively in their ability to grip, accumulate, and tolerate Cd [83]. The available literature showed significant variations in Cd tolerance between wheat species, both in bread wheat and durum wheat [12]. However, its concentration in hexaploid bread wheat is less characterized [84]. This inter-varietal variation may evolve due to differences among cultivars in Cd adsorption or uptake or agents of internal transport systems or due to the retention of Cd in different vascular tissues [85]. Furthermore, differences in Cd accumulation may also depend on the adaptation of different genotypes to environmental and production conditions [86].

In conventional breeding practices, genetic variation is created through planned or random cross combinations of genotypes. The presence of valuable genetic resources leads to the exploitation of heterotic performances evolved by the interaction of gene actions. In wheat, low-Cd cultivars are often developed by the hybridization of parental lines possessing Cd resistance ability. It has been reported that hybrid wheat showed a 10% increase in tolerance under Cd stress as compared to other traditionally used wheat cultivars [87].

We believe that conventional breeding methods have had partial success in the development of low-Cd wheat. However, with these breeding methods, breeders can only select low-Cd wheat cultivars. So far, there is no breeding strategy that has been developed for the enhancement of the Cd-resistant potential in wheat. The main obstacle for Cd breeding in wheat is the low magnitude of genetic variation. Conventional breeding practices need to create genetic variations among wheat cultivars. Once the variation is there, it provides an opportunity to select the desired genotypes—those that have an absolute expression of specific characters. Hence, conventional breeding methods typically require a tedious effort, while the complexity of the wheat genome and the time-consuming selection process inhibit the identification of low-Cd cultivars.

4.2. Marker-Quantitative Trait Loci (QTL) Analysis for Cd Toxicity in Wheat

With the advances in the production of cost-effective genome wide molecular markers, quantitative trait loci (QTL) analysis has been frequently addressed for wheat genetic mapping of Cd toxicity. In the last decades, numerous studies have been performed to identify Cd-associated QTL determining Cd uptake and stress in wheat plants. Different categories of molecular markers were used for tagging the marker-QTL of Cd resistance in wheat (Table 2). A major QTL (designated QCdu.ndsu-5B) of Cd uptake on chromosome arm 5BL within a 0.3 cM distance in durum wheat was identified with SNP markers [77]. Similarly, Penner et al (1995) detected a dominant random amplified polymorphic DNA (RAPD) marker (*OPC-20*) for low Cd uptake in western Canadian durum wheat [88]. An SNP marker (IWA1775) on chromosome 5BL was found to be associated with grain Cd content in durum wheat cultivars [89]. The associated QTL explained 54.3% of phenotypic variation, and it was further was converted to the user-friendly KASPar assay in order to discern Cd-resistant lines. Moreover, a major locus (Cdu1) on chromosome 5B conferring low grain Cd in durum wheat was mapped with an SSR marker [90]. This locus was found to be collinear with rice and *Brachypodium distachyon* through newly developed ESM markers using recombinant substitution lines (RSLs) [91].

The availability of adequately dense molecular markers in the wheat genome has been the main limitation in the identification of Cd-associated QTL. However, high-throughput genome sequencing technologies have begun to overcome this obstacle. The advent of multiplexed sequencing technology has enhanced the identification of closely linked QTL as well markers within genes/QTL controlling wheat Cd toxicity metabolism. In this regard, the high-quality reference sequence of wheat can be used as a genomic resource to accelerate wheat Cd research and breeding. Future studies may focus on the exploration of Cd-associated QTLs, paving the way for routine pyramiding [92], multiline [93], and mixture strategies to breed low-Cd wheat cultivars with the desired traits.

Table 1. Phenotypic evaluation of wheat cultivars under Cd stress.

Culture Conditions	Number of Cultivars Tested	Treatments	Toxicological Indicators	Cd Concentrations in Traits (Average) (mg kg^{-1})	Tolerant and Low-Metal Cultivars	High Accumulators	Reference
Hydroponic culture	15	0, 15, 30, and 45 µM for 2 weeks	Biomass Cd at seedling stage	51–67 (60) (shoot Cd at 15 mM treatment)	Lasani-2008 and Iqbal-2000	Sehar-2006 and Inqlab-91	[82]
Field pot culture	51	20 mg/kg for life cycle	Grain Cd	1.09–6.15 (3.5)	Ilirija	-	[31]
Hydroponic culture	10	2 nM for life cycle	Biomass and Cd among organs	0.03–0.08 µg/g (grain)	Strongfield	Dakter	[94]
Field survey	59	0.107–2.292 mg/kg	Grain Cd	0.005–0.150	Jimai518, Heng0628, Heng09, and Guan29	-	[95]
Hydroponic culture	16	1 µmol/L for 7 weeks	Growth parameters and biomass Cd	32.2-63.0 (48.1) (based on shoot dry weight)	E81513	-	[96]
Field trial	20	Around 10. 5 mg/kg	Grain Cd	0.1–0.17	Kaimai18	Zhengmai9405	[97]
Hydroponic culture	30	1 mg/L for 21 days	Seedling biomass Cd	0.91–6.74 (3.83) (shoot)	LF-13, LF-16, and LF-21 (both root and shoot)	LF-1	[98]
Hydroponic culture	2	0, 6, 30, 75, and 150 µM for 15 days	Root, shoot, and leaf traits under Cd	For BALCALI-85 shoot Cd on average was 135, and root Cd was 3371, for C1252 shoot Cd was 162 and root Cd was 1556	C-1252	-	[99]
Hydroponic culture	40	0.5 mM	Roots, flag leaf, grain, and grain coats under Cd	Cd in root on average was 29.1, in flag leaf it was 8.4, and in grains it was 2.6	-	Mjolner, Rental, Tjalve, Hanno, Grandur, and Extradur	[100]
Sand was used in thermophore plates	4	0, 5, 20, 50, and 80 mg/L	Seed germination and seedling growth	Seed germination 68.8%, germination index 6.4%, germination energy 60%, and mean germination time 5.1 days	Sehar-06	-	[101]
Hydroponic culture	3	200 µmol/L for 8 days	Root and leaf Cd	0.125 for 4 days and 0.14 for 8 days	CM42 and CM47	CY12	[102]
Hydroponic solution	2	150 µM, 200 µM, and 250 µM for 36 days	Seed germination and seedling growth	On average, 20.1% reduction was observed in NARC-11 and 23% in Galaxy	NARC-11	-	[103]
Greenhouse experiment	5	0, 25, 50, and 100 mg Cd/kg	Photosynthesis and yield characteristics	Average Cd for shoot length was 30, shoot dry weight 221, leaf area 29.6, and the net photosynthesis rate was 12.7 (mg Cd/kg)	PBW343	-	[104]
Hydroponic culture	3	0, 2, and 4 µM	Cd root morphology	Cd for shoot dry weight was 0.27 g plant-1, root dry weight was 0.14 g plant-1, root tip was 941, and total root length was 694 cm	Bakhtawar-92	-	[105]
Hydroponic culture	5	1 mg	Biomass production, yield, and yield components of wheat	Average Cd is root was 601.4, in shoot 27.8, and in grains 3.6 mg/kg	Li 667 and Ailuyuang	-	[106]
Hydroponic culture	24	50 µM for 24 days	Root and shoot parameters under Cd	Average Cd for shoot Cd concentration was 104.0, shoot Cd concentration was 1773, and total Cd accumulation was 0.055	B and D genomes cultivars showed tolerance	R genome wheat cultivars	[107]
Hydroponic culture	3	0, 0.1, 0.5, 1.0, and 2.0 µM	Shoot and root biomass, root length, and leaf area	Concentrations higher than 0.1 (imole/L) significantly decreased the traits' performances	Kyle and SC84-994	-	[85]
Hydroponic culture	3	0, 10, 20, 30, 40, and 50 µM for 24 days	Cd effect on wheat growth, leaf photon energy conversion, gas exchange, and Cd accumulation	Average Cd shoot dry weight under 6 Cd concentration was 0.27 g/plant, root dry weight 0.08 g/plant, shoot height 20.9 cm, tiller number 3.1 per plant, and secondary root number 15.6 per plant	Jing 411 and Yangmai 10	-	[108]

Table 2. Marker genotype and quantitative trait loci (QTL) analysis for low Cd in wheat.

Wheat Germplasm	Traits Investigated	Marker	Associated Marker/QTL	Breeding Technique	References
103 RIL population	13 traits of germination, growth, and physiology and 6 other traits were investigated for Cd tolerance and accumulation	A linkage map was used, constructed using different markers	26 QTL	Marker-assisted selection (MAS)	[109]
190 RIL mapping population	Grain Cd content	90K wheat SNP arrays	A single major QTL	Inclusive composite interval mapping (ICIM) method	[77]
167 RILs	Cd level	90K wheat SNP arrays	A single putative QTL	Composite interval mapping	[89]
70 F8 lines developed by the single-seed descent method	-	Random amplified polymorphic DNA (RAPD) markers	2 RAPD markers were found to be associated	MAS	[88]
155 DH lines	Grain Cd concentration	SSR markers	Cdu1 locus	MAS	[90]
155 recombinant substitution lines	Grain Cd concentration	PCR-based markers were developed for ESTs	2 ESM markers, 1 STS, and 1 minor QTL for grain Cd content were detected	MAS	[91]
155 recombinant substitution lines	Cd concentration	ESTs and STS markers	2 ESMs and 5 STS markers were identified that co-segregated with Cdu-B1	MAS	[110]
Total of 4178 advance, elite and, uniform regional durum nurseries were used	Grain Cd content	SNP markers	3 markers on chromosome 5B were found to be linked; 1 marker with Cd was polymorphic while the other 2 were not polymorphic in all of the population	MAB	[111]
14 wheat cultivars	Cd concentration	AFLP and RAPD markers	113 AFLP and 77 RAPD markers were found to be associated	MAS	[112]
2 durum wheat lines	Cd in grains	SNPs	1 QTL on chromosome 2B with 3% phenotypic variations and 1 SNP marker on chromosome 5B explaining 34% of the phenotypic variation were detected	Association mapping analysis	[113]

5. Conclusions

Cd is one of the most prevalent toxins in the environment worldwide. Its existence within soil has been acknowledged as a serious hazard to agricultural production. The excessive amount of Cd in the environment has had adverse effects on wheat growth and development. Conventional and molecular breeding strategies in wheat have been devised to minimize Cd uptake and toxicity. The potential of conventional breeding is still an attractive approach to change the Cd profile of wheat cultivars, if this is perceived as a priority. Molecular markers are powerful in the selection of wheat varieties with low Cd and other desired traits [114,115]. The manipulation of heterosis also presents new perspectives for improving wheat Cd potential and adaptation to Cd stresses. However, there remain several constraints to breeding low-Cd wheat cultivars, as it is time-consuming and the process of genetic enhancement is slow.

Modern breeding tools also lend great potential to plant breeding programs to be used along with conventional breeding for the development of low-Cd cultivars. Candidate gene and QTL identification through GWAS analysis could accelerate wheat Cd breeding programs. While genome editing tools are mature [116], molecular breeding for wheat with the desired traits is becoming a reality. Future studies may focus more on the tagging of these candidate genes with markers as well as on pyramiding these genes through MAS.

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