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REVIEW

Integrating Multi-Omics Approaches to Develop High-Yielding and Heavy Metals Stress-Resilient Crops

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ABSTRACT: Recent efforts in crop improvement have increasingly focused on elucidating molecular-level regulatory mechanisms to develop high-yielding crops with enhanced tolerance to heavy metals (HMs) stress. Omics approaches, including genomics, transcriptomics, proteomics, metabolomics, ionomics, and phenomics, provide comprehensive analyses of plant responses to HMs stress. Genomics identifies stress-responsive genes, transcriptomics reveals dynamic changes in gene expression, proteomics evaluates protein abundance and post-translational modifications, and metabolomics characterize stress-related metabolites. Ionomics elucidates essential mineral dynamics involved in detoxification, while phenomics integrate high-throughput imaging with breeding techniques to evaluate stress resilience. Integration of multi-omics approaches provides a systems-level understanding of plant responses by exploring interactions among genes, transcripts, proteins, and metabolites. Despite these advances, significant challenges remain in data heterogeneity, multi-omics integration, and predictive modeling, while updated insights and future perspectives are needed to improve stress tolerance research in plants. Emerging technologies, including CRISPR-based gene editing for functional validation, spatially resolved omics for cellular and tissue-level insights, and AI for pattern recognition and predictive modeling, are advancing the study of HMs tolerance. This review highlights the application of omics techniques in elucidating the genetic mechanisms of plant responses to HMs stress and their roles in enhancing crop resilience and productivity. Integrating these approaches provides a direct route to breeding HMs-resilient crop varieties, bridging molecular insights with farmer-ready solutions to ensure food security and safety in contaminated regions.

KEYWORDS: Omics; heavy metals stress; food security; CRISPR technology; sustainable agriculture

1 Introduction

1.1 The Global Threat of HMs and Metalloids Pollution to Crop Production

Increasing heavy metals (HMs) contamination in agricultural soils has become a major threat to crop productivity and food safety worldwide [1,2]. Rapid industrialization, mining activities, excessive use of fertilizers and pesticides, application of sewage sludge, and irrigation with contaminated wastewater have significantly increased the accumulation of toxic metals, including cadmium (Cd), lead (Pb), and mercury (Hg), as well as the metalloid arsenic (As) and selenium (Se) in agricultural soils [3,4]. Unlike organic pollutants, HMs are non-biodegradable and persist in soils for long periods, where they can disrupt soil microbial communities, alter nutrient cycling, and impair plant growth and development [5]. Their accumulation in edible plant parts not only reduces crop yield and quality but also poses serious health risks

to humans through the food chain [6,7]. Unlike previous multi-omics reviews that mainly provide dataset-oriented or metal-specific perspectives [8–10], this review integrates advances in genomics, transcriptomics, proteomics, metabolomics, and ionomics to provide a system-level, cross-metal comparative framework. It further incorporates emerging approaches such as CRISPR-based gene editing, spatially resolved omics, and AI-driven analytics to better resolve regulatory mechanisms underlying plant responses to HMs stress.

1.2 The Plants' Molecular Arsenal against HMs Stress

Plants have evolved complex physiological and molecular defense mechanisms to cope with HMs toxicity. These defense mechanisms function at multiple cellular levels and contribute to maintaining metal homeostasis and preventing the accumulation of toxic ions in sensitive cellular compartments [11]. One of the first lines of defense involves restricting metal uptake and transport, where plant cell walls, root exudates, and selective membrane transporters reduce the entry of toxic metal into the cytoplasm. Various transporter families, including ZIP, NRAMP, ABC transporters, and HMs ATPases, regulate metal influx, efflux, and redistribution in plant tissues to maintain cellular metal balance [12]. Once metals enter plant cells, they are rapidly detoxified through chelation by metal-binding molecules, particularly phytochelatins (PCs) and metallothioneins (MTs). These ligands bind toxic ions such as Cd^{2+}, Pb^{2+}, and Hg^{2+} to form stable complexes that reduce their reactivity and toxicity in the cytosol [13]. Following chelation, plants further mitigate toxicity through vacuolar sequestration and intracellular compartmentalization. Metal-ligand complexes are transported into vacuoles through tonoplast transporters, isolating them from metabolically active regions of the cell and preventing interference with essential biochemical processes [14].

HMs exposure also induces excessive production of reactive oxygen species (ROS), which can damage proteins, lipids, and nucleic acids [15]. To mitigate this oxidative stress, plants activate a complex antioxidant defense system, consisting of enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT), and peroxidases, as well as non-enzymatic antioxidants including ascorbate glutathione, carotenoids, flavonoids, and proline. These antioxidants scavenge ROS and restore cellular redox homeostasis [16,17]. In addition to their damaging effects, ROS function as key signaling molecules that interact with calcium (Ca^{2+}), nitric oxide (NO), and phytohormones such as abscisic acid (ABA), salicylic acid (SA), jasmonic acid (JA), and ethylene (ET). This signaling crosstalk activates MAPK cascades and stress-responsive transcription factors (TFs), including MYB, WRKY, NAC, and bZIP families, which regulate genes involved in metal transport, antioxidant defense, phytochelatin, and metallothionein biosynthesis, and vacuolar sequestration [4,18]. Collectively, the integration of uptake regulation, metal chelation, sequestration, antioxidant defense, and signaling-mediated detoxification forms a coordinated molecular arsenal that enables plants to tolerate and adapt to HMs-contaminated environments [19].

1.3 Global Food Security under HMs Stress

Recent global assessments estimate that approximately 14–17% of the world's cropland, equivalent to about 242 million hectares, is contaminated with toxic metals above safety thresholds, potentially affecting 900 million to 1.4 billion people worldwide [5]. The global food demand is expected to increase by >50% in 2050 [20]. In addition to a significant reduction in agricultural productivity, the accumulation of toxic metals in edible plant tissues poses serious risks to human health, particularly in developing countries where contaminated soils are widely cultivated [21]. Conventional breeding and single-omics approaches are insufficient to address the complex genetic and physiological mechanisms involved in HMs tolerance, detoxification, and accumulation [22]. The integration of multi-omics technologies with systems biology and precision genome editing offers unprecedented opportunities to unravel these complex regulatory

networks and accelerate the development of high-yielding crop varieties that maintain productivity on contaminated soils while minimizing HMs accumulation in edible tissues [23]. Such integrated strategies are essential for simultaneously improving crop productivity, food safety, and agricultural sustainability in contaminated soils [24]. Therefore, this review synthesizes current advances in multi-omics research and presents a forward-looking framework for translating molecular insights into breeding and biotechnological strategies that enhance crop resilience and safeguard future food security.

1.4 The Limitations of Single-Omics Approaches

Advances in high-throughput molecular technologies have significantly improved our understanding of plant responses to HMs stress. Genomics provides comprehensive genetic information about an organism and helps identify genes potentially involved in metal transport, detoxification, and stress signaling [25]. Transcriptomics further reveals gene expression patterns under stress conditions and provides insights into regulatory pathways activated during HMs exposure. However, these approaches are insufficient to fully explain plant stress responses at the phenotypic level [6,26]. Gene expression does not always correlate with protein abundance or enzymatic activity, and metabolic changes often occur independently of transcriptional regulation. The plant response is an integrated outcome of dynamic interactions among multiple molecular layers, including genes, transcripts, proteins, and metabolites [27,28]. Therefore, systems biology, facilitated by multi-omics integration, provides a comprehensive approach to unravel this complexity [29]. Importantly, integrating multi-omics data with high-throughput phenotyping and quantitative trait loci (QTL) mapping enables the precise identification of key genetic loci associated with HMs tolerance and yield stability, supporting marker-assisted breeding and genome selection strategies [30]. Such integration also guides precise genome editing, such as CRISPR-Cas9, to modulate stress-responsive genes without affecting growth under normal conditions [31]. Furthermore, coupling omics with rhizosphere and microbial studies facilitates the development of bioinoculants that enhance stress tolerance while maintaining crop productivity [32]. These approaches collectively provide practical pathways to develop HMs-tolerant crops without compromising yield (Fig. 1).

1.5 Scope and Aims of This Review

In the era of high-throughput biology, multi-omics integration has emerged as an effective strategy for exploring complex stress-response mechanisms in plants. This review critically discusses recent advancements in each omics field in the context of HMs stress in plants. Moreover, it proposes a conceptual framework for integrating diverse omics datasets to better understand the regulatory mechanisms and pathways associated with HMs tolerance. This review also highlights successful examples of multi-omics integration and discusses future challenges and opportunities, including the potential use of artificial intelligence (AI) and gene editing technologies such as CRISPR-based approaches to develop crops with enhanced HMs tolerance and reduced metals accumulation.

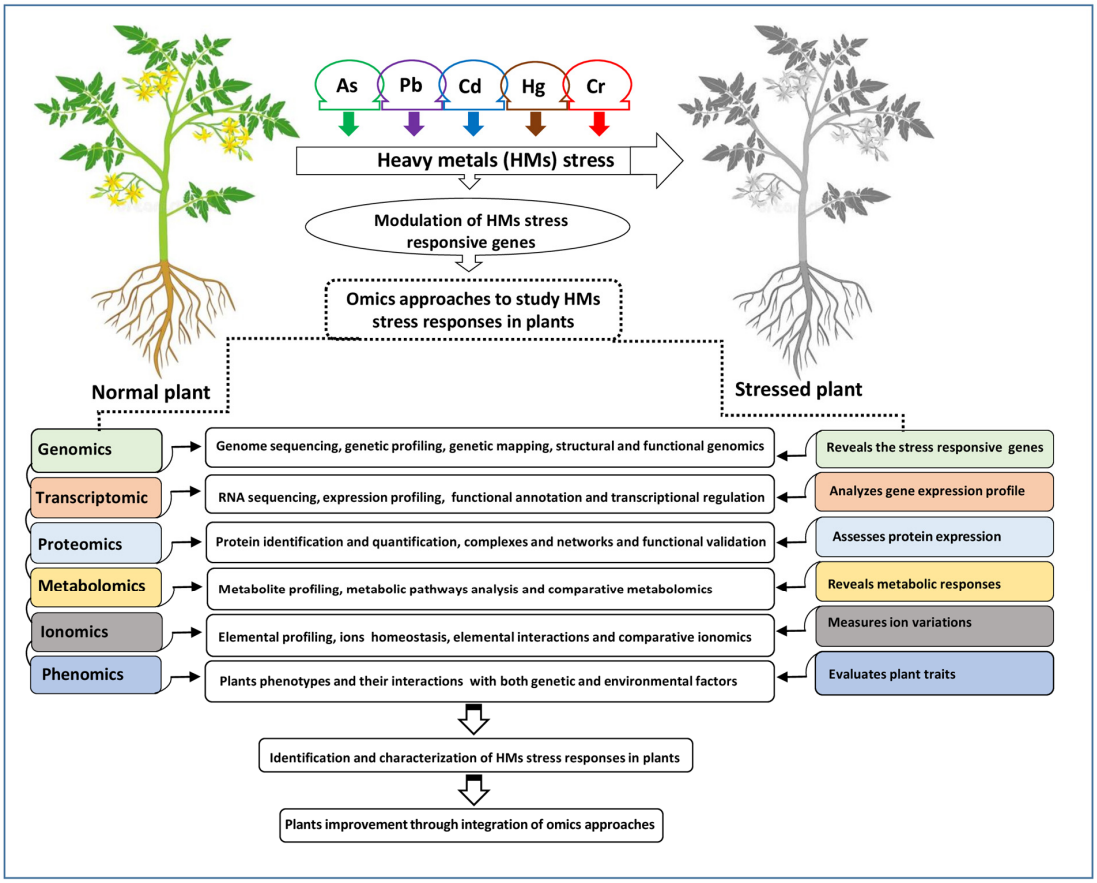

Figure 1: An integrated omics framework for understanding and mitigating HMs stress in plants. The diagram compares normal and HMs-stressed plants and highlights the role of genomics (stress-responsive genes), transcriptomics (gene expression), proteomics (protein profiles), metabolomics (metabolic changes), ionomics (elemental homeostasis), and phenonomics (plant traits) in elucidating HMs tolerance mechanisms and supporting crop improvement.

2 The Multi-Omics Toolbox: Deconstructing the Plant Response

2.1 Genomics: Identifying the Genetic Blueprint for Tolerance

Genomics analysis is fundamental to understanding plant responses to HMs stress and involves the complete set of genes, transcription factors (TFs), and regulatory sequences involved in stress adaptation [6]. Plants have evolved sophisticated mechanisms to resist HMs toxicity through a complex network of stress response pathways involving both protein-coding and non-coding regulatory genes, as well as various physiological and biochemical processes that contribute to detoxification and tolerance [33]. Therefore, the sequencing and annotation of these genes through genomic approaches are critical for crop improvement and the advancement of phytoremediation strategies [34]. Genome-wide analyses have identified key gene families involved in HMs homeostasis, such as Heavy Metal ATPases (HMAs), Zinc-regulated transporters, Iron-regulated transporter-like proteins (ZIPs), Cation Diffusion Facilitators (CDFs), and Natural Resistance-Associated Macrophage Proteins (NRAMPs), which are crucial for HMs uptake, transport, and sequestration [35]. For example, HMA4 transport plays a critical role in loading Zn and Cd into the xylem for subsequent translocation to shoots [36]. Similarly, ABC transporters are involved in transporting metal-phytochelatin complexes into vacuoles for sequestration [37]. Plant responses to HMs stress are

primarily controlled at the genomic level by cis-regulatory DNA sequences, delayed response genes like TFs, and the organization of chromatin structure [38].

With the availability of vast amounts of sequencing data from multiple plant varieties, it is important to develop effective computational methods to characterize and annotate this data. Databases and computational analyses are extensively used in genomics studies for various purposes, including sequence analysis, gene identification, phylogenetic analysis, heterologous analysis, exon-intron organization, chromosome positioning, gene ontology, and function studies, cis regulator investigation and analysis of 5′ and 3′ untranslated regions [39–41]. Comprehensive databases like Gramene (http://www.gramene.org/), Phytozome (https://phytozome-next.jgi.doe.gov), PlantGDB (http://www.plantgdb.org/), EnsemblPlants (http://plants.ensembl.org/), and VISTA (http://genome.lbl.gov/vista/index.shtml) are available in addition to species-specific databases like TAIR (http://www.arabidopsis.org), riceDB (https://rapdb.dna.affrc.go.jp/), MaizeGDB (https://www.maizegdb.org/) and SoyBase (https://www.soybase.org/). These databases provide user-friendly interfaces and are valuable for the retrieval of plant genes and their orthologous sequences. Existing work has applied these resources to genome-wide gene family analyses in plants [42,43]. For example, Phytozome provides a platform for comparative genomic analysis, allowing researchers to identify conserved and divergent genetic components across plant species [44]. Functional genomics approaches can then be used to characterize the functional roles of genes identified through these analyses [45] (Fig. 2).

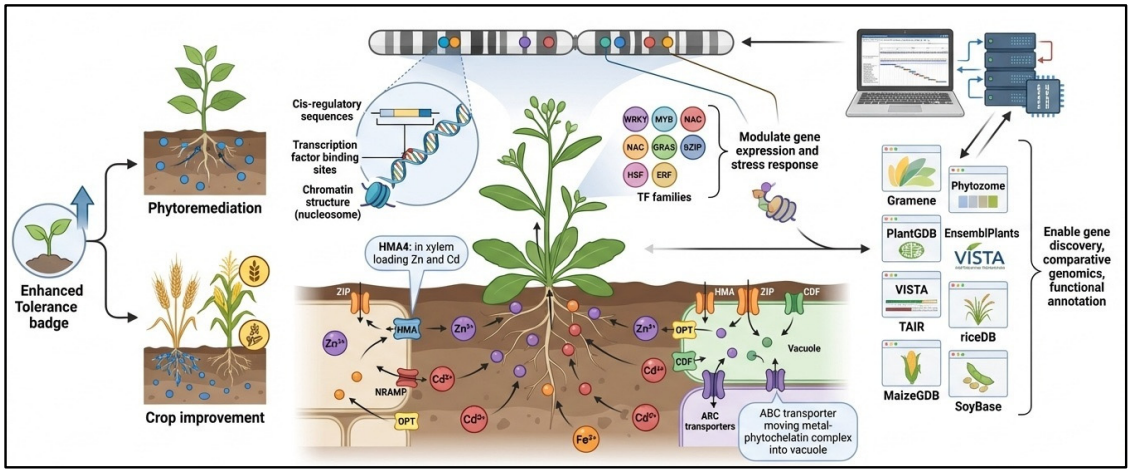

Figure 2: Schematic representation of a multi-level genomic framework for enhancing plant resilience and phytoremediation potential. The diagram illustrates genomic regulation through cis-regulatory elements, transcription factor binding sites, and chromatin organization in stress-responsive gene expression. It also depicts key transport mechanisms involved in HMs uptake and sequestration, mediated by HMA4, NRAMP, and ABC transporters involved in vacuolar sequestration of metal phytochelatin complexes. In addition, it illustrates the application of bioinformatics databases (Gramene, Phytozome, TAIR, and MaizeGDB) for gene discovery and functional annotation, supporting phytoremediation and crop improvement.

Genome-wide studies have identified and characterized many key genes involved in metal stress responses and tolerance mechanisms in various plant species, particularly in hyperaccumulators. For example, 26 genes in *Nicotiana tabacum* [46], 20 genes in *Triticum aestivum* [47], 18 genes in *Brassica rapa* [48], 12 MTP genes in *Arabidopsis thaliana* [49], 11 genes in *Vitis vinifera* [50], 22 genes in *Populus trichocarpa* [51], 12 genes in Citrus sinensis [52], and 10 genes in *O. sativa* [53]. Similarly, understanding the regularity roles of TFs families such as *WRKY*, *MYB*, *NAC*, *GRAS*, *bZIP*, *HSF* and *ERF* provides valuable

insights for improving phytoremediation strategies and developing crops with enhanced tolerance to metal contaminated environments [54,55]. For example, MYC2 and MYB43 TFs cooperatively repress the expression of the *HMA2* and *HMA4* genes, resulting in the regulation of Cd tolerance in *A. thaliana* [36]. Furthermore, studies on the OPT (oligopeptides transporter) gene family have shown its role in maintaining intracellular metal homeostasis, with 94 OPT genes identified in different plant species, including 21 in potato (*Solanum tuberosum*) [56]. However, it is important to recognize that the genome represents the potential for tolerance, a static framework that requires dynamic regulation to be manifest as a functional phenotype [6]. Despite these advances, most genomic studies have been conducted under controlled laboratory and greenhouse conditions, limiting their direct applicability to field environments. Therefore, candidate genes require validation through multi-environment field trials and integration with multi-omics approaches before reliable application in crop improvement and phytoremediation.

2.2 Transcriptomics: Deciphering the Dynamic Gene Expression Landscape

Transcriptomics, primarily using RNA sequencing (RNA-seq), is instrumental in elucidating the genetic components that are actively expressed or suppressed under HMs stress, as well as their temporal and tissue-specific expression patterns [57]. The transcriptome, representing the complete set of RNA transcripts in a specific cell or tissue under defined physiological conditions, provides a dynamic profile of gene activity [58]. While genomics techniques reveal the presence or absence of specific target genes, transcriptomics is essential for elucidating their functional roles through expression analyses [59]. Transcriptome profiles provide useful insights for understanding how an organism responds to specific physiological states or stress conditions, as the transcriptome varies depending on factors such as tissue type, developmental stage, and environmental conditions [58]. In the context of HMs stress, this variability is significantly influenced by sampling time and tissue specificity, with roots often exhibiting earlier and stronger transcriptional responses compared to shoots, leading to variation in expression patterns across experiments [60]. For example, plants subjected to HMs stress exhibit significant transcriptional reprogramming, leading to differential expression of genes involved in metabolic pathways and survival mechanisms [61]. Studies have shown that HMs exposure induces changes in the expression of genes related to stress signaling, ROS detoxification, and cell wall modification [26,62]. For example, genes involved in sulfur assimilation, glutathione metabolism, and vesicular trafficking are often found in conserved co-expression modules under various HMs stresses [7].

In addition to these functional genes, regulatory genes such as TFs play an important role in regulating stress response genes by forming complex gene networks [54]. Through transcriptome analysis and computational techniques, several TF families, including WRKY, MYB, ARF, bZIP, NAC, bHLH, HSF and Dof TFs have been identified and characterized in various plant species such as rice, cucumber, *Arabidopsis*, and Glycyrrhiza, which exhibit diverse regulatory responses to abiotic stressors, including HMs [63–66]. For example, our previous study conducted comparative genomic and transcriptomic analyses, revealing significant changes in the expression of WRKY and bHLH TFs in response to Cd stress in *Solanum lycopersicum* [39]. Comparative biochemical and transcriptional profiling of *S. lycopersicum* treated with Cd has further elucidated the mechanisms by which plants perceive and tolerate such toxin-induced stress [67] (Fig. 3).

Transcriptomics analysis has been used to investigate Cd tolerance in cotton plants [68], and a multi-omics approach has been employed to elucidate the essential roles of subcellular reallocation in Cd resistance in rapeseed [69]. Infiltration-RNAseq, a recently developed technology, integrates RNA-seq and TF agroinfiltration to rapidly and efficiently detect TF-mediated transcriptional changes and

associated transcripts [70]. Co-expression network analysis derived from transcriptomic data can be used to predict gene functions and identify regulatory hubs involved in responses to HMs [7,71]. For example, stress responsive TFs from the WRKY family regulate the activation of structural genes initially identified through genomic analyses [6]. Similar transcriptomic frameworks have also been applied to other major toxic metals such as Pb, Hg, and Cr, indicating common regulatory responses across multi-metal stress conditions [62]. Moreover, variability in RNA-seq datasets due to biological replication, sequencing depth, library preparation methods, and environmental conditions often affects transcriptome reproducibility across studies, emphasizing the need for standardized experimental design and robust statistical normalization approaches [72]. The transient nature of transcriptional responses and the imperfect correlation between transcript and protein levels highlight the need to integrate multiple omics approaches for a comprehensive understanding HMs tolerance mechanisms [73].

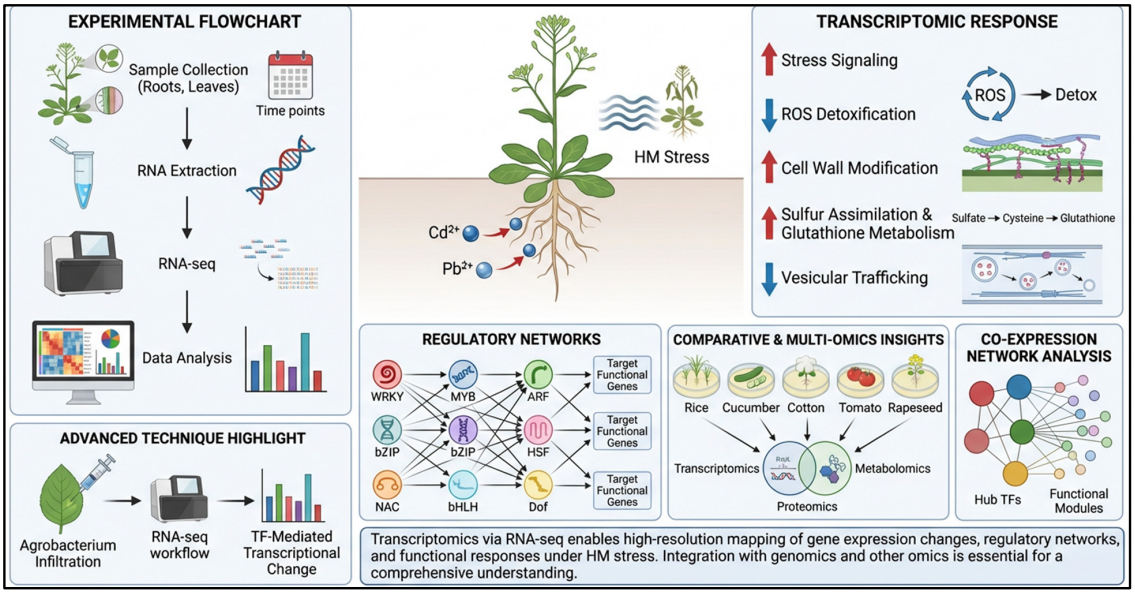

Figure 3: This figure illustrates a comprehensive transcriptomic analysis of plants under HMs stress. The experiential pipeline includes sample collection, RNA extraction, RNA-seq, and data analysis. It highlights key transcriptomic changes such as stress signaling, cell wall modification, and sulfur/glutathione metabolism, along with altered ROS detoxification and vesicular trafficking. The figure also illustrates transcription factor-mediated regulatory networks (WRKY, bZIP, MYB, NAC) and integration of transcriptomic, proteomic, and metabolomic data across crops. Additionally, it shows experimental validation approaches such as Agrobacterium-mediated assays for confirming transcription factor-regulated gene expression.

2.3 Proteomics: From Transcript to Functional Machinery

Proteomics has recently emerged as a valuable tool for understanding plant responses to diverse environmental conditions, including HMs stress, and provides insights into changes in protein abundance, activity, and post-translational modifications following transcriptomics analyses [74,75]. In particular, it enables the identification of post-translational modifications (PTMs) that rapidly modulate protein function [7,76]. Techniques such as two-dimensional gel electrophoresis (2-DE), mass spectrometry (MS)-based proteomics, and iTRAQ studies have significantly advanced this field [7]. A key insight from proteomics is the frequent observation of discrepancies between mRNA and protein levels, indicating that transcript abundance does not always directly correlate with protein levels due to complex post-transcriptional and translational

regulation. This emphasizes the need to validate transcriptomic findings at the protein level to gain a more accurate understanding of the functional machinery [73]. PTMs, such as phosphorylation, can rapidly activate or deactivate proteins, providing swift responses to HMs toxicity that are not revealed by transcriptomics analyses. For example, redox enzymes, including ascorbate peroxidase (APX), and glutathione reductase (GR), often exhibit discrepancies between transcript and protein levels, indicating the importance of translational regulation and rapid PTMs in HMs stress responses [77]. Advanced proteomic approaches, including mass spectrometry, two-dimensional gel electrophoresis, and computational proteomics [78], provide comprehensive insights into protein responses under HMs stress and contribute to strategies for improving plant stress tolerance [6]. PTM-based approaches, such as phosphoproteomics and ubiquitomics have become increasingly important in plant stress biology. Phosphoproteomics enables the identification of phosphorylation-mediated signaling events involved in stress perception and signal transduction [79], whereas ubiquitomics reveals ubiquitin-dependent protein turnover through the ubiquitin-proteosome system, regulating the stability of stress-responsive proteins [80]. Proteomics studies have revealed the involvement of various proteins in HMs stress responses, including those associated with stress signaling, antioxidant defense, and metal binding [7,81]. Specific proteomic analyses have further elucidated these mechanisms (Fig. 4).

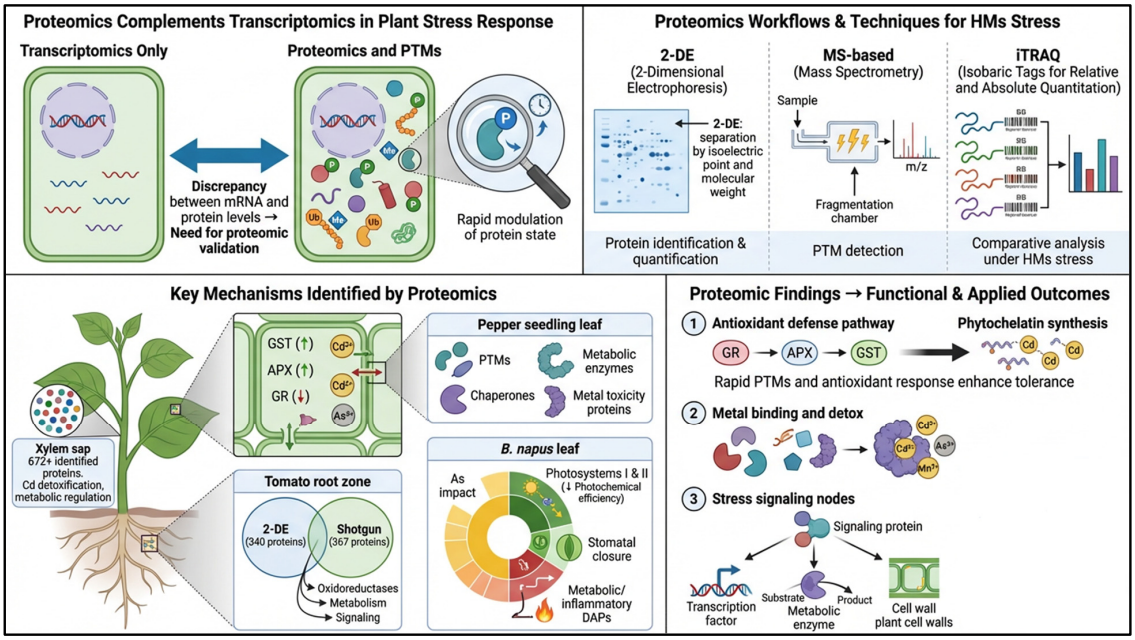

Figure 4: This figure illustrates the integration of proteomics with transcriptomics to understand plant responses to HMs stress. The top-left panel shows how proteomics bridges mRNA-protein differences to validate gene expression. The top-right panel depicts key workflows, including 2-DE for separation and MS-based techniques (e.g., iTRAQ) for identification and quantification. The bottom-left panel highlights tissue specific mechanisms in xylem sap and tomato roots, focusing on metal detoxification and metabolic regulation. The bottom-right panel shows functional outcomes, including antioxidant defense, metal binding, and stress signaling modulation.

For example, a proteomic analysis of xylem sap in Cd-treated rapeseed plants revealed approximately 672 proteins that influence metabolic pathways related to protein/lipid metabolism, stress/oxidoreductases, and cell wall modification [82]. Recent xylem sap proteomic studies revealed that plant defensins play a positive role in enhancing Cd tolerance in *B. napus* [83]. Another study reported that exposure of

maize seedlings to 200 mg/l $CdCl_2$ results in alterations of the root proteome and significant growth inhibition within 72 h. The study identified proteins with varying abundance levels, including glutathione-S-transferase (GST) GRMZM2G308687, which exhibited elevated levels after Cd treatment, suggesting its role in synthesizing phytochelatins to improve Cd tolerance [84]. Proteomic analysis of pepper seedlings treated with selenium (Se) revealed the upregulation of 172 and the downregulation of 28 proteins. This study identified differentially abundant proteins (DAPs) associated with post-translational modifications, chaperones, metabolic activities, protein turnover and processing, as well as responses to metal toxicity [85]. Ceballos-Laita et al. (2018) investigated the effects of manganese (Mn) toxicity on tomato root proteome using two complementary proteomic techniques. The 2-DE technique identified 340 consistent protein spots, whereas the shotgun approach identified 367 proteins, with the primary metabolic pathways affected including oxidoreductases, protein metabolism, and signaling [86]. The response of *B. napus* cultivars ZS758 and ZD622 to high As concentrations was investigated using iTRAQ-based proteomics analysis. The results indicated that As stress significantly reduced the photochemical efficiency of photosystems I and II and induced stomatal closure [87]. Numerous genes associated with metabolic pathways and As-responsive-DAPs were identified in the ZS758 and ZD622 cultivars exposed to As stress [88].

2.4 Metabolomics: Capturing the Chemical Phenotype

Metabolomics provides a functional perspective of the plant's physiological state under HMs stress by integrating the cumulative effects of genetic and proteomics changes on its metabolic profile [73,77]. It is an advanced approach, widely used to generate comprehensive datasets and applicable to a broader range of studies compared to other omics techniques. This technique provides detailed insights into plant internal processes and their responses to varying environmental conditions [89]. Plant metabolites are molecules with a mass of less than 2000 Da. By 2018, the KNApSAcK database cataloged approximately 51,000 metabolites identified from higher plants, out of an estimated 200,000 to 1,000,000 primary and secondary metabolites in the plant kingdom [90,91]. The metabolomics approach can be used to construct a network of metabolites under stress conditions, which can then be used in crop development programs. This information can be applied to metabolomics-assisted breeding, transgenic plant development, phenotypic analysis, drug discovery and extraction, mutation characterization, and other related fields [92].

This approach includes the analysis of primary metabolites, such as proline and glutathione (GSH), as well as secondary metabolites, including flavonoids and phenolics. These molecules play critical roles in ROS scavenging, metal chelation, and the regulation of signaling pathways [93]. For example, proline accumulates in response to stress, functioning as both an osmoprotectant and an antioxidant. This well-characterized metabolite plays multiple roles in plants, including the activation of antioxidant enzymes and metal chelation, and is commonly used to develop transgenic plants with enhanced tolerance to HMs stress [94]. Similarly, putrescine has been applied to enhance HMs stress resistance in crops [95]. GSH serves as a precursor for phytochelatins, which are essential for HMs detoxification [75]. In *Arabidopsis*, alpha-tocopherol levels increase under Cd stress, suggesting its role as a stress-relieving mechanism [96]. Ascorbate and glutathione are other key metabolites involved in responding to ROS stress and mitigating metal toxicity [97]. Some secondary metabolites, such as tannins, phenols, carotenoids, and flavonoids, activate antioxidant enzymes, mitigate ROS accumulation under HMs stress, and protect the photosynthetic machinery by regulating ROS generation [94] (Fig. 5).

Metabolomics approaches can be broadly categorized into targeted and untargeted strategies. Targeted metabolomics focuses on the precise quantification of predefined metabolites with high sensitivity and accuracy, making it particularly useful for hypothesis-driven studies of specific stress related pathways [98].

In contrast, untargeted metabolomics provides a comprehensive, unbiased profiling of metabolites, enabling the discovery of novel biomarkers and previously unknown metabolic changes under stress conditions [99]. Together, these complementary approaches enhance both the depth and breadth of metabolic insights in HMs stress studies [100]. Importantly, metabolomics has been strengthened by metabolite flux analysis and stable isotope labelling approaches, which enable the tracking of dynamic metabolic pathways and carbon and nitrogen fluxes under stress conditions, providing a more accurate understanding of metabolic reprogramming beyond steady-state metabolite levels [101].

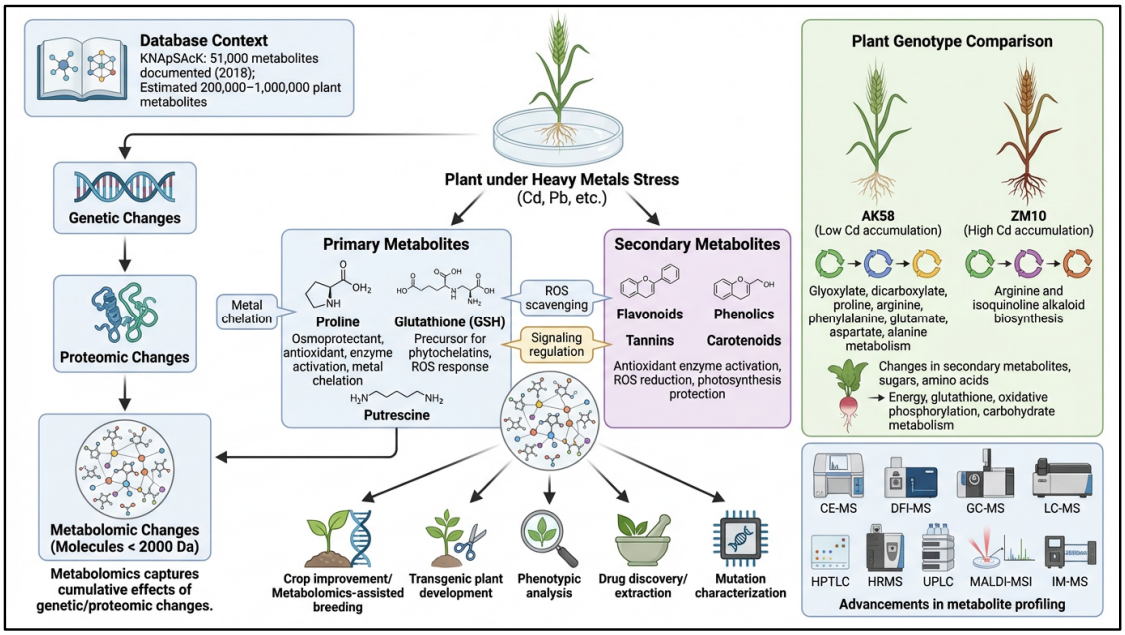

Figure 5: Schematic representation of plant responses to HMs stress. The diagram illustrates the cascade from genetic and proteomic alterations to metabolomic reprogramming and subsequent phenotypic outcomes relevant to crop improvement. It highlights the accumulation of primary metabolites, such as proline and glutathione, involved in metal chelation and secondary metabolites such as flavonoids and tannins involved in ROS scavenging. The figure also compares metabolic profiles between genotypes (AK58 and ZM10) differing in Cd accumulation and outlines key analytical platforms (GC-MS, LC-MS, UPLC, and MALDI-MSI) for metabolite profiling, along with their applications in metabolomics-assisted breeding, transgenic development, metabolite-based discovery, and mutation characterization.

Studies have demonstrated distinct metabolomic profiles in plant genotypes with different HMs accumulation capabilities. For example, two wheat genotypes, AK58 (Aikang58, a genotype with low Cd accumulation in grains) and ZM10 (Zhenmai10, a genotype with high Cd accumulation in grains), exhibit distinct metabolomic profiles in their roots under Cd stress [102]. KEGG analysis identified six common potential pathways associated with the antioxidant defense system in both ZM10 and AK58 genotypes. These pathways include the metabolism of glyoxylate, dicarboxylate, proline, arginine, phenylalanine, glutamate, aspartate, and alanine, as well as the biosynthesis of arginine and isoquinoline alkaloids [102]. Radish roots exposed to Cd and Pb exhibit alterations in secondary metabolites, sugars, amino acids, and other metabolites, and KEGG pathway analysis highlights changes in carbohydrate metabolism, glutathione metabolism, and oxidative phosphorylation-related pathways [103]. The characterization and quantification of metabolites have progressed significantly due to improvements in instrumentation and the application of core principles from techniques such as mass spectrometry and chromatography. Currently, combined tools

like capillary electrophoresis-MS (CE-MS), direct flow injection-MS (DFI-MS), gas chromatography-MS (GC-MS), and liquid chromatography-MS (LC-MS) are being developed for plant metabolome profiling [104]. Depending on specific requirements and the type of characterization, other instruments such as high-performance thin-layer chromatography (HPTLC), high-resolution mass spectrometry (HRMS), ultra-performance liquid chromatography (UPLC), matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI), and ion mobility mass spectrometry (IM-MS) are also commonly used [105,106].

2.5 Ionomics: The Elemental Composition as an Integrative Readout

Plants require appropriate levels of minerals to maintain their essential cellular processes. These minerals, known as ionomes, are required in trace amounts for normal plant growth and development, as well as for the detoxification of toxic metals and metalloids [107]. Ionomics, a high-throughput elemental profiling method, measures the elemental composition of plant tissues, providing a top-down perspective on how HMs stress influences the uptake, accumulation, and distribution of both essential and non-essential elements [76,108]. This approach helps to understand nutrient interactions; for example, calcium (Ca) and nitrogen (N) nutrition can cooperatively alleviate Cd toxicity by influencing transport mechanisms [108]. Ionomics provides insights into the mechanisms by which plant transport and homeostasis systems, regulated by gene networks identified through genomics and transcriptomics, regulate metal uptake and distribution [37]. For example, multi-omics integration in the hyperaccumulating ecotype of *Sedum alfredii* Hance has elucidated the zinc metabolic regulatory network, demonstrating the complexity of metal homeostasis in these plants [109] (Fig. 6).

N is an essential component of proteins, vitamins, hormones, nucleic acids, and other biomolecules. It also plays a crucial role in the synthesis of chlorophyll, nitrogen-containing antioxidants, and metabolites that mitigate the toxicity of hazardous metals and metalloids [10,110]. N supplementation has been reported to enhance plant growth and stress tolerance under Cd [111], whereas the N-rich amino acid asparagine combined with thiourea significantly enhances Pb tolerance in wheat by regulating the AsA-GSH cycle, Pb detoxification, and N metabolism [112]. Similarly, nitrate (NO_3^-) has been shown to improve tolerance to Hg stress [113] in different plant species, mainly through improved antioxidant defense and metabolic regulation. Cd toxicity in Sedum plants was decreased by the application of 16 mM N fertilizer ($(NH_4)_2SO_4$) [114]. When *Solanum nigrum* was treated with $(NH_4)_2SO_4$ and CH_4N_2O, plant biomass increased by up to 2.0 and 2.1 times, respectively, compared to the control plants under Cd stress (2 mg/kg) [115]. Magnesium (Mg), an essential component of chlorophyll (Chl), enhances the activity of antioxidant enzymes by reducing Cd toxicity. Foliar application of Mg increased root growth by 32%, essential oil production by 17%, leaf area by 24%, chlorophyll contents by 10%, and soluble sugar synthesis by 33%, while also decreasing lipid peroxidation and osmotic stress [116]. Ca plays a significant role in plant metabolic activities and helps mitigate the toxicity of toxic metals and metalloids [117]. Ca treatment has been shown to ameliorate Cd toxicity by enhancing antioxidant capacity and stabilizing cell membranes, leading to reduced Cd uptake and translocation within plant tissues [118].

Research on ionomics in rice seedlings has demonstrated that nano-silicon priming (SiNP) effectively reduces fluoride uptake and bioaccumulation, enhancing fluoride tolerance. This approach promotes safer rice cultivation by improving photosynthetic activity and mineral nutrient uptake while mitigating oxidative damage [119]. Additionally, a study on rice grains and straw identified 70 new ionomic QTLs associated with 15 nutritional elements. This study further revealed that the *qMo8* QTL, which regulates molybdate content in both grain and straw, is controlled by the molybdate transport gene *OsMOT1;1* [120]. Rice plants cultured in nutrient solutions supplemented with As (III) at concentrations of 100 and 500 μg/L exhibited distinct

ionomic responses under different environmental conditions. The results showed that As (III) significantly influenced the binding, transport, and metabolic regulation of essential elements, including P, K, Ca, Zn, and Cu. Furthermore, the study revealed a strong correlation between the transcriptome and ionome in rice shoots. Analysis of As (III) treated rice shoots identified 3812 differentially expressed genes (DEGs) compared to controls, with key functions related to transmembrane transport and ion binding, indicating that rice plants respond to As toxicity by reallocating additional nutrients [121]. Another study validated these findings, demonstrating that transcriptomic and ionomic approaches can elucidate the relationship between gene regulation and ionome homeostasis in rice under As stress [122]. However, nutrient supplementation strategies may also induce physiological trade-offs, as excess or imbalanced nutrient supply can disrupt ion homeostasis through antagonistic and synergistic interactions among elements and alter metabolic allocation under stress conditions, potentially affecting overall plant growth and stress adaptation efficiency [123]. For example, excess phosphorus application has been widely reported to reduce Zn uptake due to P-Zn antagonism in *Salvia hispanica* [124]. Similarly, Ca, Si, and Mg supplementation can mitigate HMs toxicity by reducing metal uptake and improving membrane stability in rice, although their effects on micronutrient homeostasis may vary depending on concentration and environmental conditions [125].

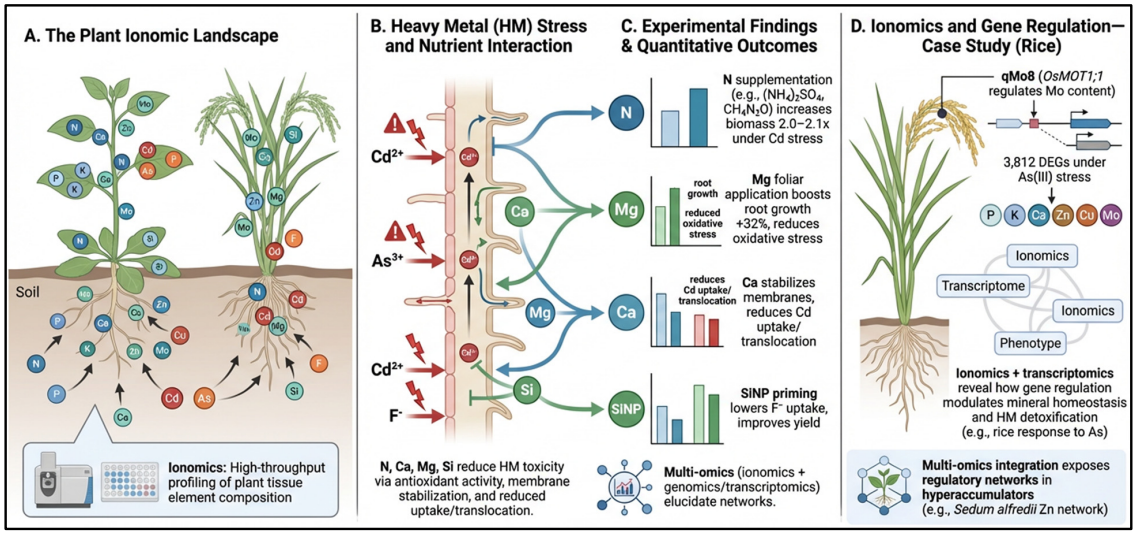

Figure 6: The role of ionomics and multi-omics integration in understanding plant responses to HMs stress. (**A**) Plant ionomic landscape: high-throughput profiling of elemental composition highlights uptake of essential nutrients (N, P, K, Ca) and toxic elements (Cd, As) from the soil. (**B**) HMs stress and nutrient interaction: beneficial elements (N, Ca, Mg, Si) mitigate toxicity by stabilizing membranes and reducing the uptake or translocation of harmful ions. (**C**) Experimental outcomes: Nutrient supplementation enhances biomass, promotes root growth, and reduces HMs uptake through SiNP priming. (**D**) Ionomics and gene regulation: In rice and hyperaccumulators, integrating ionomics with transcriptomics and phenotyping identifies gene regulators and DEGs controlling mineral homeostasis and HMs detoxification.

2.6 Phenomics: Bridging the Gap between Genotype and Stress Response

Phenomics bridges the gap between molecular and biochemical changes and whole-plant phenotypes, including growth, biomass, and yield [27,76]. This multidisciplinary field utilizes various tools to assess plant morphological, physiological, and behavioral traits, integrating genomic procedures with breeding techniques to understand metabolic pathways in stress-tolerant crop varieties [126]. High-throughput phenotyping (HTP) technologies, such as advanced imaging, spectroscopy, and 3D laser scanning, enable

non-destructive assessment of plant traits under various stress conditions [127]. Phenomics plays a crucial role in genome-wide association studies (GWAS) and QTL mapping by linking specific genetic variations to stress-resilient traits. For example, UAV-based multispectral imaging combined with deep learning has been used to predict grain Cd accumulation in rice [27]. Advancements in genomics and bioinformatics have significantly enhanced phenomics and analytical techniques, thereby enabling more precise assessment of genotype-environment interactions and the identification of specific plant phenotypes [128]. In the post-genomic era, there is a significant emphasis on phenomics, particularly with the implementation of techniques such as genomic selection GS), marker-assisted selection (MAS), GWAS, and QTL mapping, that primarily depend on HTP to enhance crop productivity. These approaches have facilitated the identification of genomic regions and candidate genes involved in HMs tolerance. However, HMs tolerance is a complex polygenic trait influenced by environmental conditions and interactions between genotype and environment [129]. Conventional biparental QTL mapping is limited by low mapping resolution and restricted allelic diversity, whereas GWAS may be affected by population structure, rare alleles, and limited power to detect loci with small effects [130]. Moreover, many identified QTLs and marker-trait associations lack consistency across diverse genetic backgrounds and environments, restricting their application in breeding [131]. Therefore, integrating GWAS and QTL analyses with HTP, multi-omics, and functional validation is increasingly recognized as an effective strategy for the identification of robust loci controlling complex traits [132]. HTP technologies enable the collection of large datasets through automated digital analysis, ensuring accurate data processing and interpretation using robust statistical techniques [133]. Crop breeding integrates phenomics with other omics techniques to identify plants with the most desirable phenotypes, offering a promising strategy for achieving agricultural sustainability by considering plant responses to various stresses, including metal and metalloids toxicity [82]. Several studies highlight the application of phenomics in stress research. For example, the effects of salt stress on maize seedlings were investigated using an advanced high-throughput phenotypic platform equipped with a 3D laser sensor. The study assessed growth responses, identified critical periods of phenotypic variations, and conducted dynamic GWAS to identify important genes associated with salt resistance in maize seedlings [134]. In another study, a high-throughput rice phenotyping facility (HRPF) was developed to reveal traits related to rice morphology, biomass, and yield throughout the growing season and after harvest. Integrating HRPF with GWAS demonstrated that high-throughput phenotyping has the potential to replace traditional phenotyping approaches, serving as a new tool for plant genetics, genomics, genetic characterization, and breeding research [135] (Table 1).

Despite rapid advances in plant phenomics, the implementation of HTP platforms faces practical and infrastructural challenges, particularly in developing countries. High initial investment costs for imaging systems, sensor networks, and automated platforms, along with substantial expenses for maintenance and calibration, limit their widespread adoption in resource-limited research programs [136]. In addition, the establishment of controlled environment facilities and field-deployable phenotyping infrastructure requires significant financial and technical capacity, which is often constrained in developing regions [137]. Another major limitation is the shortage of trained personnel with expertise in sensor technologies, image analysis, and computational phenotyping workflows, which restricts efficient data acquisition and interpretation [138]. Furthermore, HTP generates large, high-dimensional datasets that require advanced computational infrastructure and bioinformatics pipelines for storage, processing, and analysis, which are often not readily available in low-resource settings [136].

Table 1: Summary of key genes, TFs, metabolites, and omics tools involved in plant responses and tolerance mechanisms to HMs stress in different crop species.

Category	Component	Function in HMs Tolerance	Example Crop/Species	Associated Metals	Omics/Tool Used	Reference
Genes (Transporters)	*HMA4*	Xylem loading of Zn/Cd; metal translocation	*Arabidopsis thaliana*	Cd, Zn	Genomics	[36]
	ZIP family genes	Metal uptake and transport regulation	Multiple crops	Cd, Pb, Zn	Genomics/Transcriptomics	[139]
	NRAMP genes	Metal uptake and homeostasis	Rice, maize, *Arabidopsis*	Cd, Pb, Fe	Genomics	[140]
	ABC transporters	Vacuolar sequestration of metal–chelate complexes	Rapeseed, *Arabidopsis*	Cd, Pb	Proteomics/Genomics	[12]
	HMA genes	Heavy metal efflux and detoxification	Various crops	Cd, Pb, Zn	Genomics	[36]
Transcription Factors (TFs)	WRKY TFs	Regulate stress-responsive and detoxification genes	Rice, tomato, cotton	Cd, Pb, Hg	Transcriptomics	[39,141]
	MYB TFs	Control antioxidant and metal homeostasis genes	*Arabidopsis*, tomato	Cd, Pb	Transcriptomics	[4,142]
	NAC TFs	Regulate ROS detoxification and stress signaling	Rice, wheat	Cd, Cr	Transcriptomics	[143,144]
	bZIP TFs	Regulate redox and stress signaling pathways	Multiple crops	Cd, Pb, Hg	Transcriptomics	[145]
	HSF/ERF TFs	Heat and metal stress cross-regulation	Multiple crops	Cd, Pb, Cr	Transcriptomics	[146]
Metabolites	Glutathione (GSH)	Chelation precursor for phytochelatins	Rice, *Arabidopsis*	Cd, Pb, Hg	Metabolomics	[75].
	Phytochelatins (PCs)	Metal chelation and detoxification	Multiple crops	Cd, Pb, Hg	Metabolomics	[147]
	Proline	Osmoprotection and ROS scavenging	Wheat, maize	Cd, Pb	Metabolomics	[148]
	Flavonoids/phenolics	Antioxidant defense and ROS detoxification	Tomato, rice	Cd, Cr, Hg	Metabolomics	[148,149]
	Ascorbate–glutathione cycle	Redox homeostasis maintenance	Multiple crops	Cd, Pb, Hg	Metabolomics	[148]

Table 1: *Cont.*

Category	Component	Function in HMs Tolerance	Example Crop/Species	Associated Metals	Omics/Tool Used	Reference
Proteins/Enzymes	SOD, CAT, APX, GR	ROS detoxification enzymes	Rice, maize, rapeseed	Cd, Pb, Hg, Cr	Proteomics	[150]
	GST (glutathione-S-transferase)	Detoxification and conjugation	Maize, rapeseed	Cd, Pb	Proteomics	[151]
	Metallothioneins (MTs)	Metal binding and sequestration	*Arabidopsis*, rice	Cd, Hg	Proteomics/Genomics	[152,153]
Omics Tools	RNA-seq/ Transcriptomics	Gene expression profiling under HMs stress	Cotton, rice	Cd, Pb, Hg, Cr	Transcriptomics	[154]
	Co-expression network analysis (WGCNA)	Identification of regulatory hubs	Multiple crops	Cd, Pb	Transcriptomics	[155]
	Proteomics (iTRAQ)	Protein abundance and analysis	Maize	Cd	Proteomics	[156]
	Metabolomics (GC-MS, LC-MS, CE-MS)	Metabolic reprogramming under stress	Wheat, radish, *Arabidopsis*	Cd, Pb	Metabolomics	[103]
	Ionomics (ICP-MS)	Elemental redistribution and homeostasis	Rice, Wheat	Cd, Pb, As	Ionomics	[8,157]
	CRISPR-Cas systems	Functional validation of tolerance genes	Rice, *Arabidopsis*	Cd, Pb	Functional genomics	[158]
	Spatial omics (MALDI-MSI)	Tissue-specific metal/metabolite mapping	Rice	Cd	Spatial ionomics	[159]

3 Challenges, Bottlenecks, and Future Directions in Multi-Omics Research

Multi-omics approaches have revolutionized biological research by integrating diverse datasets to provide a comprehensive understanding of complex biological systems. This integrative approach is particularly valuable for elucidating complex biological processes, such as plant responses to environmental stressors like HMs contamination [62]. However, the field still has substantial challenges and bottlenecks, primarily regarding data integration, the transition from correlation to causation, and the continued advancement of technologies required to achieve deeper biological insights [160,161].

3.1 The Data Integration Bottleneck

A principal challenge in multi-omics research is managing the large volume and inherent heterogeneity of the generated datasets [160]. Although high-throughput technologies have significantly advanced data generation efficiency, the subsequent processes of data storage, standardization, and effective integration of heterogeneous datasets remain significant bottlenecks [162,163]. Integrating transcriptomic data with metabolomic or ionomic datasets requires advanced computational tools and well-standardized analytical pipelines to ensure comparability and accurate interpretation [164]. To address these challenges, several computational frameworks have been developed for multi-omics data integration. For example, Weighted Gene Co-expression Network Analysis (WGCNA) identifies co-expressed molecular modules associated with phenotypic traits, but is primarily limited to correlation-based relationships [165]. Similarly, Multi-Omics Factor Analysis (MOFA) applies a Bayesian latent factor model to identify shared and data-specific factors of variation across multiple omics datasets [166]. In contrast, Similarity Network Fusion (SNF) integrates diverse omics datasets by fusing sample similarity networks to enable robust sample stratification [167]. DIABLO (Data Integration Analysis for Biomarker discovery using Latent variable approaches for Omics studies), implemented in the mixOmics framework, identifies correlated multi-omics biomarkers that discriminate predefined biological groups [168]. In addition, machine learning approaches, including random forests, support vector machines (SVMs), and deep learning, can integrate heterogeneous datasets and capture complex nonlinear patterns. However, they generally require large, high-quality datasets and may have limited interpretability [169]. Moreover, different omics platforms often generate data in diverse formats with different sensitivities, resolutions, and technical biases, which further complicate their harmonization and integrated analysis [170]. Consequently, without robust and efficient data integration strategies, the full potential of multi-omics approaches to elucidate complex biological interactions and regulatory networks remains limited [162].

3.2 From Correlation to Causation: The Need for Functional Validation

Multi-omics studies are effective in identifying correlations among various molecular layers [171]. For example, these approaches can reveal associations between transcriptomic and metabolomic changes under HMs stress. However, it is important to note that correlation does not indicate causation [172]. Moreover, transcriptomic and proteomic datasets often show poor correlation because mRNA abundance does not always reflect protein levels due to post-transcriptional regulation, differences in translation efficiency, protein turnover, and post-translational modifications [173]. To address these limitations, integrative computational frameworks combining transcriptomic, proteomic, and metabolomic data through network-based analyses and machine learning have been increasingly used to identify key regulated pathways [174]. Importantly, moving from correlation to causation requires experimental validation using complementary approaches, including CRISPR-Cas based gene knockouts and overexpression studies to directly test gene function, analyses of natural variation, and GWAS to link genetic variants with phenotypic traits [175,176].

Additional approaches include time-series experiments to resolve causal temporal dynamics, heterologous expression systems to validate gene function in controlled backgrounds [177], and Mendelian randomization approaches to infer causal effects from genetically anchored variation [178]. Determining the functional significance of these identified associations is an essential step in multi-omics research. Many multi-omics analyses identify candidate genes, proteins, or metabolites potentially involved in a particular stress response; however, direct experimental validation is necessary to confirm their functional roles [179]. This often involves elucidating the genetic and biochemical mechanisms involved in plants' stress responses, which underlies the differences in stress tolerance and adaptation among plant species [180]. For example, ionomic analyses can reveal changes in elemental composition under stress conditions, while transcriptomic studies can identify differentially expressed genes. However, functional validation is required to determine whether a specific gene directly regulates the transport or sequestration of a particular ion [181]. HMs stress responses are not limited to protein-coding genes, as non-coding RNAs, including microRNA (miRNAs) and long non-coding RNAs (lnRNAs), play key roles in post-transcriptional regulatory networks [182]. These RNAs modulate gene expression through mRNA degradation or translational inhibition, thereby regulating genes involved in metal uptake, transport, and homeostasis. For example, miR156 targets SPL (SQUAMOSA PROMOTER BINDING PROTEIN-LIKE) genes under HMs stress in *Arabidopsis*, while miR398 contributes to Cu homeostasis by regulating ROS-related genes [4]. Similarly, exposure to As and Cu^{2+} triggered oxidative stress and significantly reduced the induction of miR395 compared with wild-type *Arabidopsis* [183].

3.3 Emerging Technologies and Future Frontiers

The future direction of multi-omics research is increasingly influenced by emerging technologies with the potential to overcome current limitations and provide new opportunities for scientific discovery.

3.3.1 Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning (ML) are increasingly important tools for analyzing and interpreting the complex, high-dimensional datasets generated by multi-omics platforms. These computational approaches enable the identification of complex patterns and the development of predictive models from multi-omics datasets that are often difficult to detect through human analysis [184]. AI and ML algorithms can significantly facilitate the integration of heterogeneous datasets, effectively manage missing values, reduce data noise, and identify key biomarkers or genetic networks associated with specific traits, such as HMs tolerance in plants [185]. For example, supervised learning algorithms such as random forest (RF), support vector machines (SVM), and partial least squares regression (PLSR) have been widely applied for trait prediction and feature selection in plant stress studies, including the identification of metal stress-responsive biomarkers from multi-omics and phenotypic datasets [186,187]. For example, deep learning algorithms combined with unmanned aerial vehicles (UAV)-based multispectral imaging have been successfully used to predict Cd accumulation in rice grains, demonstrating the potential of AI in high-throughput phenomics [188,189]. In addition, convolutional neural networks (CNNs) have been applied for image-based phenotyping tasks such as leaf trait estimation and stress classification, while ensemble learning approaches have improved the robustness of genotype-phenotype prediction models under variable environmental conditions [190].

3.3.2 CRISPR-Based Gene Editing for Functional Validation

Clustered regularly interspaced short palindromic repeats (CRISPR)-based gene editing technologies provide a precise and efficient approach for the functional validation of candidate genes identified through

multi-omics studies [191]. Through targeted knock-outs, insertions, or modifications of genes such as *OsNRAMP5*, *OsLCT1*, *OsNRAMP1*, and *OsHAK1* in rice using CRISPR/Cas systems, researchers can directly investigate the roles of specific genes in stress responses, including tolerance to HMs [31,192]. *OsNRAMP5* mediates root uptake of Cd and Mn [193], while *OsLCT1* is involved in HMs transport from xylem to phloem [194]. CRISPR-mediated disruption of these genes has been shown to significantly reduce HMs accumulation in rice grains. These functional outcomes demonstrate that CRISPR-based validation links transcriptome-derived candidate genes with phenotypic effects, bridging the gap between correlation-based multi-omics findings and causal functional roles in HMs uptake and tolerance [195]. For example, if multi-omics analyses identify a transporter protein gene involved in Cd sequestration, CRISPR can be used to modify this gene and subsequently observe its impact on Cd uptake and distribution within the plant. In addition to single-gene editing, multiplex CRISPR approaches have been developed to simultaneously target multiple regulatory genes, enabling trait stacking for enhanced HMs tolerance [196]. Such strategies are particularly important for balancing the reduction of toxic metals accumulation with the maintenance of essential micronutrient homeostasis [197]. However, the application of CRISPR-edited crops also raises important biosafety, regulatory, and ethical considerations. Potential concerns include unintended off-target mutations, ecological impacts resulting from gene flow to wild relatives, and long-term environmental safety [198]. Regulatory frameworks for genome-edited crops vary across countries, with some treating certain CRISPR-derived plants similarly to GMOs, while others apply product-based regulation depending on the absence of foreign DNA [199]. In addition, ethical discussions focus on transparency, public acceptance, and responsible deployment of genome editing technologies in agriculture, particularly in food crops. Addressing these issues is essential for the safe and sustainable application of CRISPR technology in crop improvement [200].

3.3.3 Spatially Resolved Omics

Traditional omics approaches analyze bulk tissue samples, which inherently average out spatial variations in molecular profiles [159]. In contrast, emerging spatially resolved omics techniques, including spatial transcriptomics and metabolite imaging such as MALDI-MSI, introduce a critical spatial dimension to biological understanding [201]. These advanced technologies enable the analysis of gene expression and metabolite distribution within specific cells or distinct tissue regions, providing detailed insights into localized responses to stress [202]. Understanding the precise cellular location of HMs accumulation or detoxification mechanisms can reveal novel strategies to enhance plant tolerance. For example, spatial ionomics has been used to investigate ions distribution across different rice organs under Cd stress, revealing spatially specific responses and contributing to the development of improved crop varieties [159]. High resolution spatial ionomics reveals nutrient and HMs distribution within plant organs, such as the preferential sequestration of manganese (Mn) in specific *A. thaliana* cell types, which limits shoot toxicity and provides detailed insights into plant adaptive strategies [203]. The detailed elemental profiling provided by ionomics, especially when combined with spatial resolution, can significantly enhance our understanding of elemental dynamics and their complex relationship with genetic regulation in response to various stressors. For example, high-resolution ionomic profiling of *Populus trichocarpa* leaves identified numerous genomic loci associated with variation in elemental composition [204]. These advancements in multi-omics research, particularly through the integrated application of AI/ML, CRISPR-based gene editing, and spatially resolved omics, are expected to accelerate the discovery of novel mechanisms underpinning stress tolerance in plants, ultimately enabling the development of more resilient and productive agricultural systems.

3.3.4 Plant-Microbe Interactions in HMs Stress Adaptation

Rhizosphere and endophytic microbial communities play a central role in modulating HMs availability, mobility, and plant tolerance within the soil-plant system. These microbes can reduce metal toxicity through multiple mechanisms, including metal sequestration, biosorption, chelation, precipitation, and transformation, as well as by enhancing plant antioxidant defenses and stress-responsive metabolism [205]. Recent studies have shown that plant growth-promoting rhizobacteria (PGPR) and endophytes can significantly improve plant resilience under HMs stress by altering rhizosphere chemistry and reducing metal bioavailability. In the context, rhizosphere and endophytic microbiomes are increasingly recognized as key regulators of plant adaptation to contaminated environments, with their functional roles extending beyond nutrient acquisition to direct involvement in detoxification and stress mitigation [206]. Importantly, advances in multi-omics approaches have enabled detailed characterization of plant-microbe interactions and the identification of microbial genes and pathways associated with metal resistance and homeostasis [207]. Accordingly, integrating host multi-omics data with rhizosphere and endophytic metagenomics and metabolomics is emerging as a powerful approach to decipher plant holobiont responses to HMs stress [208].

4 Conclusion

The integration of omics approaches has significantly advanced our understanding of plant responses to HMs stress. Genomics and transcriptomics elucidate gene expression and regulatory networks, while proteomics and metabolomics reveal adaptive biochemical and metabolic changes. Ionomics provides insights into nutrient-metal interactions, and phenomics integrates molecular changes with whole-plant phenotypic traits, facilitating the selection and breeding of stress-tolerant crops. Despite these advances, considerable challenges remain, particularly in managing data heterogeneity, effective integration, and translating observed correlations into functional roles. Emerging technologies, including CRISPR-based gene editing for functional validation, high-resolution spatial omics for cellular and tissue-level insights, and AI/ML for pattern recognition and predictive modeling, provide effective strategies to address these limitations. The continued integration of multi-omics approaches with CRISPR, AI, and ML enables precise identification of key genes, regulatory networks, and elemental dynamics associated with HMs tolerance. Future research should prioritize field validation under realistic environmental conditions to ensure translational relevance, investigation of temporal dynamics of stress responses to capture causal progression, and expansion of multi-omics studies to orphan and underutilized crops to enhance global agricultural applicability. In addition, socio-economic integration will be essential to support technology adoption in farming systems, and the development of user-friendly computational platforms will be crucial to enable accessible multi-omics analysis for non-specialist users. A coordinated interdisciplinary framework integrating plant biology, computational sciences, breeding programs, and socio-economic research is therefore essential to translate multi-omics discoveries into practical solutions for sustainable agriculture and global food security.

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