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INTEGRATIVE MULTI-OMICS INSIGHTS INTO HEAVY METAL STRESS TOLERANCE IN AMARANTHUS: TOWARDS SUSTAINABLE PHYTOREMEDIATION AND NUTRACEUTICAL CROP DEVELOPMENT

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Abstract *Amaranthus spp. has great potential as a nutritionally complete, climate-resilient crop that is suited for cultivation on marginal or contaminated soils. However, the continuing increase in the amount of toxic heavy metals i.e., cadmium (Cd), lead (Pb), and arsenic (As) present within soils, is a major limiting factor for crop productivity, food safety, and environmental sustainability. Recent advances in high-throughput omics technologies, which have produced system-level insights related to plant responses to stress, have not been effectively applied to amaranth. This review summarizes current scientific knowledge concerning the molecular mechanisms that underlie the ability of Amaranthus spp. to tolerate heavy metal stress through the use of integrative multi-omics strategies. These tolerance strategies include metal transport, chelation, antioxidant defense, and stress signaling, and will be considered through the lens of systems biology to illustrate how these mechanisms are coordinated with one another. A review of the current state of genomics, transcriptomics, proteomics, and metabolomics research revealed critical issues with data integration, functional validation, and species-specific resources. Constraints such as low genetic diversity, low transformation efficiency, and multi-omics data integration difficulties are discussed. Future directions highlighted the integration of multi-omics with genome editing techniques and artificial intelligence to accelerate the development of heavy metal-tolerant and nutritionally-enhanced amaranth cultivars, thereby supporting sustainable agricultural systems and resilient food systems.*

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Introduction

The presence of heavy metals in agricultural land has become an environmental and agricultural issue with substantial consequences on crop yield and food security (Bello et al., 2021; Tóth et al., 2016). The non-biodegradable nature of toxic substances, such as arsenic (As), cadmium (Cd), and lead (Pb), causes these substances to accumulate in crops and enter the food chain, thereby exposing people to these toxins (Chowdhury and Rahman, 2024). Physiologically, heavy metals disrupt homeostasis at the cellular level, inhibiting photosynthesis by disrupting the integrity of cellular membranes; they also generate excessive reactive oxygen species (ROS), causing oxidative stress, which ultimately restricts growth (Hoque et al., 2021; Mansoor et al., 2023).To withstand metal toxicity, plants have developed sophisticated methods of defending themselves through mechanisms such as restricting their uptake of metal ions from the soil, sequestering metals within their cells after they are taken up into their bodies, and activating pathways to detoxify metals (Bhat et al., 2025; Ioniţă et al., 2026). The effectiveness of these mechanisms to counteract metal toxicity can vary greatly between different plant species and among individual plants in the same species (i.e., genotypes) (Aslam et al., 2021; Raza et al., 2022).

Amaranthus spp., a climate-resilient and nutritionally dense crop, with high levels of protein, essential amino acids, and micronutrients, has received increasing attention from scholars studying plant stress adaptation (Segura-Jiménez and Jacobo-Velázquez, 2025; Yadav and Yadav, 2024). However, little is known about the molecular mechanisms that confer stress tolerance to amaranth under heavy metal stress conditions. Omics technologies have changed how we study plants and how we do plant biology. Genomic research provides us with valuable information about the gene itself, such as how each gene is structured or how different genes vary from one another (Kress et al., 2022; Wainstein et al., 2023). Transcriptomic research has provided us with the ability to analyze the expression levels of genes at different time points and during stress (Peng et al., 2023; Xing et al., 2024). The complementary capabilities of proteomics and metabolomics are helping us understand the physical dynamics of proteins and how they change metabolically during stress. Integrating these types of datasets via a systems biology approach allows us to develop more holistic models of entire stress-induced networks, creating exceptional opportunities for enhancing crops (Moshood et al., 2025; Qi et al., 2026). Thus, omics technologies are revolutionizing how we study plants and the fields of plant biology.

Molecular Basis of Heavy Metal Stress Tolerance

Regulation of metal uptake and transport happens through specialized membrane transporters in plant roots as the mechanism for heavy metal-stress tolerance (Hussain et al., 2024; Ningombam et al., 2024). This type of transport and uploading protein families are: Heavy Metal ATPases (HMAs), Natural Resistance-Associated Macrophage Proteins (NRAMP), and Zinc-iron Permease (ZIP) transporters that play a large role in the influx, efflux, and internal metal ion distribution (Liu et al., 2024; Rekha et al., 2021). Accumulation is maintained by preventing excessive uploading of ions through selective uploading via different types of molecular transporters in each type of tissue (Samodelov et al., 2020). Heavy metals are detoxified by chelation with low-molecular-weight compounds (ligands) like phytochelatins and metallothioneins once they're inside a cell. The integrated processes of uptake, chelation, and sequestration are illustrated in Figure 1A–B.

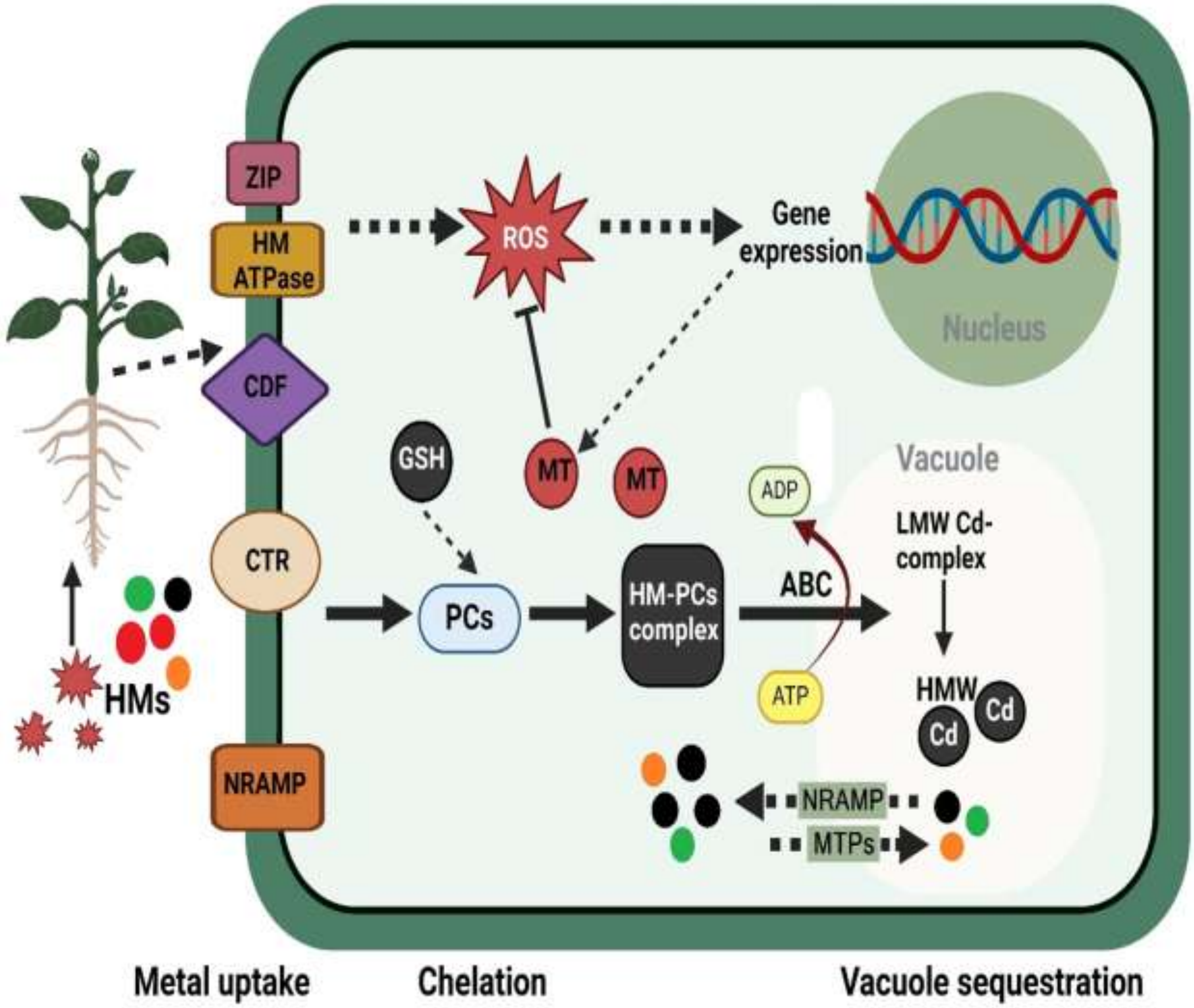

Figure 1A. Schematic representation of heavy metal (HM) detoxification mechanisms in plant cells, showing metal uptake, chelation by PCs and MTs, vacuolar sequestration via ABC and MTP transporters, and regulation by gene expression and ROS signaling.

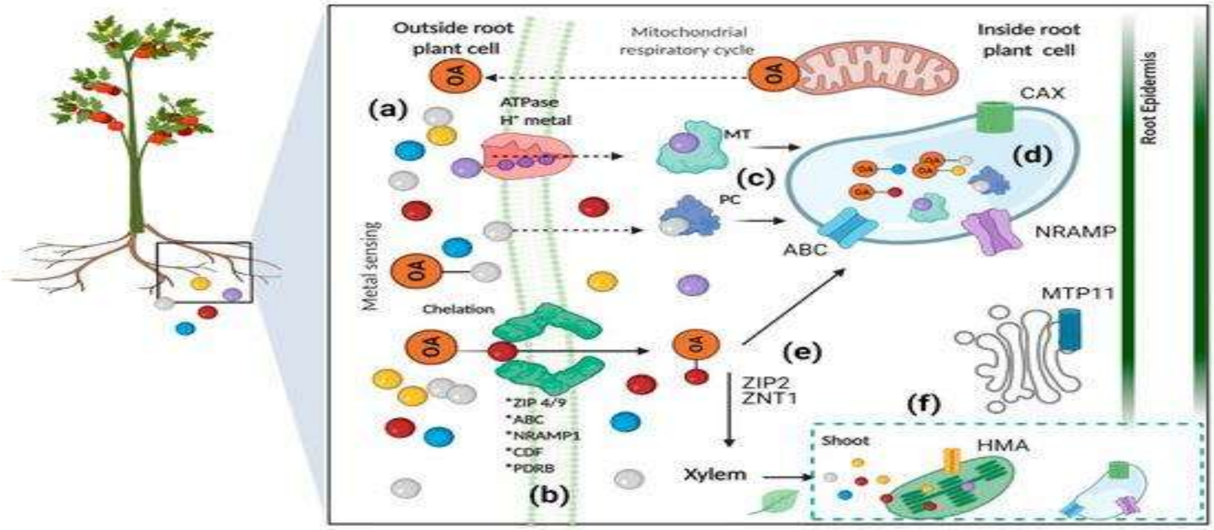

Figure 1B. Heavy metal transport and detoxification pathways in plants, including root uptake, xylem loading for shoot translocation, and cellular mechanisms such as chelation, vacuolar sequestration, and metal sensing

They form stable complexes with toxic metal ions by binding them, which are then sequestered into vacuoles by ATP-binding cassette (ABC) transporters (Agarwal et al., 2022; Galahitigama et al., 2025). This compartmentalization of the heavy metals prevents them from interfering with essential metabolic processes. An important indicator of heavy metal stress is the overproduction of reactive oxygen species, which requires the development of effective antioxidant defenses. In addition to non-enzymatic molecules such as ascorbate and glutathione, enzymatic antioxidants—including catalase, superoxide dismutase, and peroxidase—are all used together to maintain redox balance (Ali et al., 2019; Ansari et al., 2024). When stress is perceived at the regulatory level, a series of complex signaling cascades is triggered that involves calcium ions and phytohormones (e.g., abscisic acid), as well as mitogen-activated protein kinase pathways. These pathways activate transcription factors (i.e., the MYB, WRKY, and bZIP families) to coordinate the expression of stress-responsive genes (Mohanta et al., 2018; Ravi et al., 2023) (Figure 2). Although the mechanisms mentioned above have been well studied in model plants, they are still poorly understood for Amaranthus spp., which shows that this topic is an area needing more research.

Current Status of Omics Research in Amaranthus spp.

Omics technologies have made inconsistent progress in *Amaranth* spp. (Amaranthaceae), With genomics providing the strongest foundation and under development in other areas of omics. There are a few high-quality whole-genome assemblies for Amaranth spp. Most notably, the available genomes provide an excellent resource for comparative genomics and gene discovery for *A. hypochondriacus* and other related species (Lightfoot et al., 2017; Zhao et al., 2021). The existence of these genomic datasets has allowed the identification of transcripts that are related to abiotic stress, transcription factors, stress-related molecular markers, and agronomically important traits. Transcriptional studies of amaranth are few, and only recently have they begun to assess the gene expression profile response associated with abiotic stressors. Early work has identified transcripts linking to osmotic and oxidative stress response (ion transport, osmotic regulation, and oxidative stress response) associated with abiotic stress response; however, there are no comprehensive analyses of the transcripts associated with heavy metal stress (Lancíková et al., 2020; Xie et al., 2019).

Proteomics is a new field of study that started out focusing primarily on analyzing the proteins of seeds as well as making comparisons among different types of seeds (Miernyk and Hajduch, 2011). It has begun to provide researchers with evidence suggesting that post-translational modifications may play an important role in helping plants adapt to environmental stresses; however, whether or not post-translational modifications contribute to plant tolerance to metal stress is still uncertain (Srivastava et al., 2025). Metabolomics has been able to demonstrate that there are huge discrepancies in the composition of different types of metabolites produced by different species of plants, as well as when looking at the same plant species grown in different environmental conditions (Cho et al., 2025). The accumulation of certain osmoprotective metabolites (proline and trehalose) is indicative of changes to the overall metabolism of a plant due to the stress of environmental conditions that may ultimately result in improved levels of stress tolerance (Nawaz et al., 2022) (Figure 3). Unfortunately, one of the greatest barriers in bringing together the large amounts of metabolomic data with genomic, transcriptomic and phenotypic (physiological) data is the difficulty of integrating these different levels of information into one coherent model.

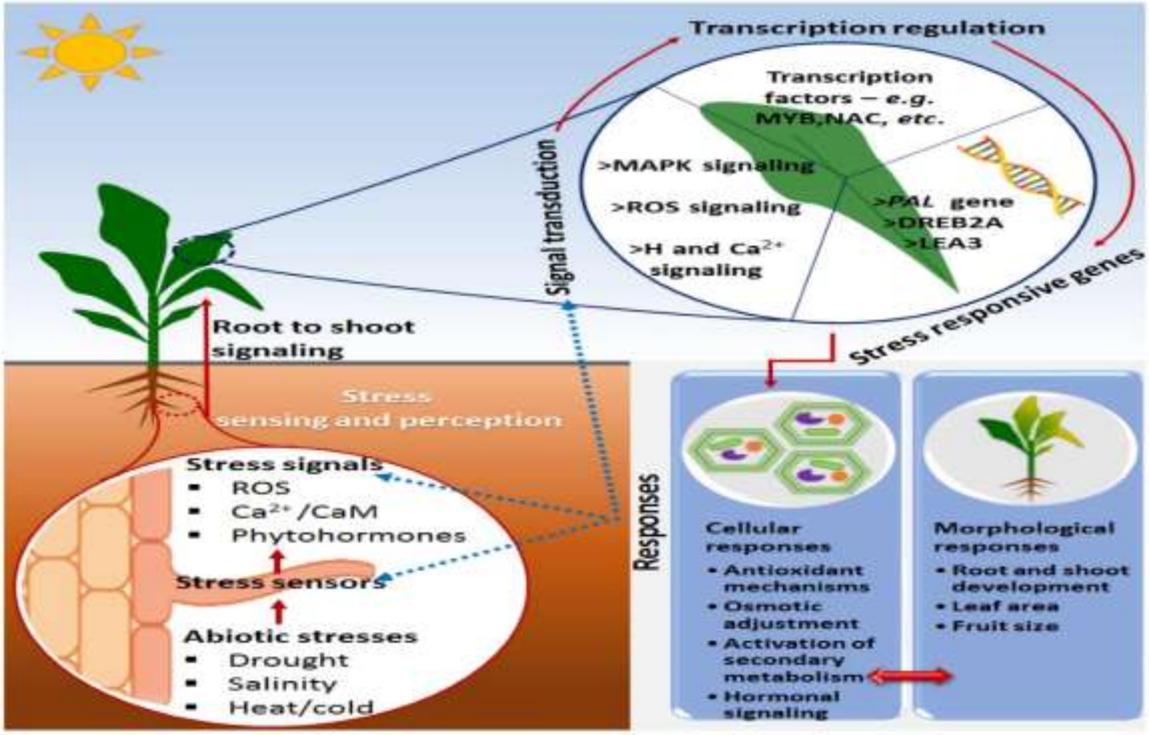

Figure 2. Schematic representation of abiotic stress signaling and transcriptional regulation in plants, from stress sensing and signal transduction (MAPK, ROS, Ca^{2+}) to transcription factor activation (MYB, NAC) and downstream cellular/morphological responses

Table 1. Multi-Omics Integration for Heavy Metal Stress Resilience in *Amaranthus*: From Molecular Insight to Breeding Application

Omics Layer	Biological Insight	Mechanistic Relevance to Heavy Metal (Cd, Pb, As) Stress	Translational Application
Genomics	Gene architecture, structural variants, SNPs, QTLs	Identification of metal transporter genes (e.g., *NRAMP*, *HMA*, *ZIP*), natural variation in chelation and vacuolar sequestration pathways	Genome-wide association studies (GWAS), marker-assisted selection (MAS), genomic prediction
Transcriptomics	Temporal and tissue-specific gene expression dynamics	Discovery of metal-responsive regulatory networks, ROS signaling hubs, and phytohormone crosstalk (ABA, JA, ET)	Candidate gene prioritization for CRISPR editing, stress-inducible promoter engineering
Proteomics	Protein abundance, post-translational modifications (PTMs), protein-protein interactions	Functional validation of metal detoxification enzymes (PC synthase, SOD, CAT, APX), redox homeostasis, and metal chelation complexes	Targeted proteome remodeling, marker development for stress tolerance
Metabolomics	Primary and secondary metabolite profiling	Quantification of metal-chelating ligands (PCs, GSH, organic acids, flavonoids), osmotic adjustment, and oxidative stress signatures	Metabolic engineering, biomarker-assisted screening, and nutraceutical quality assurance

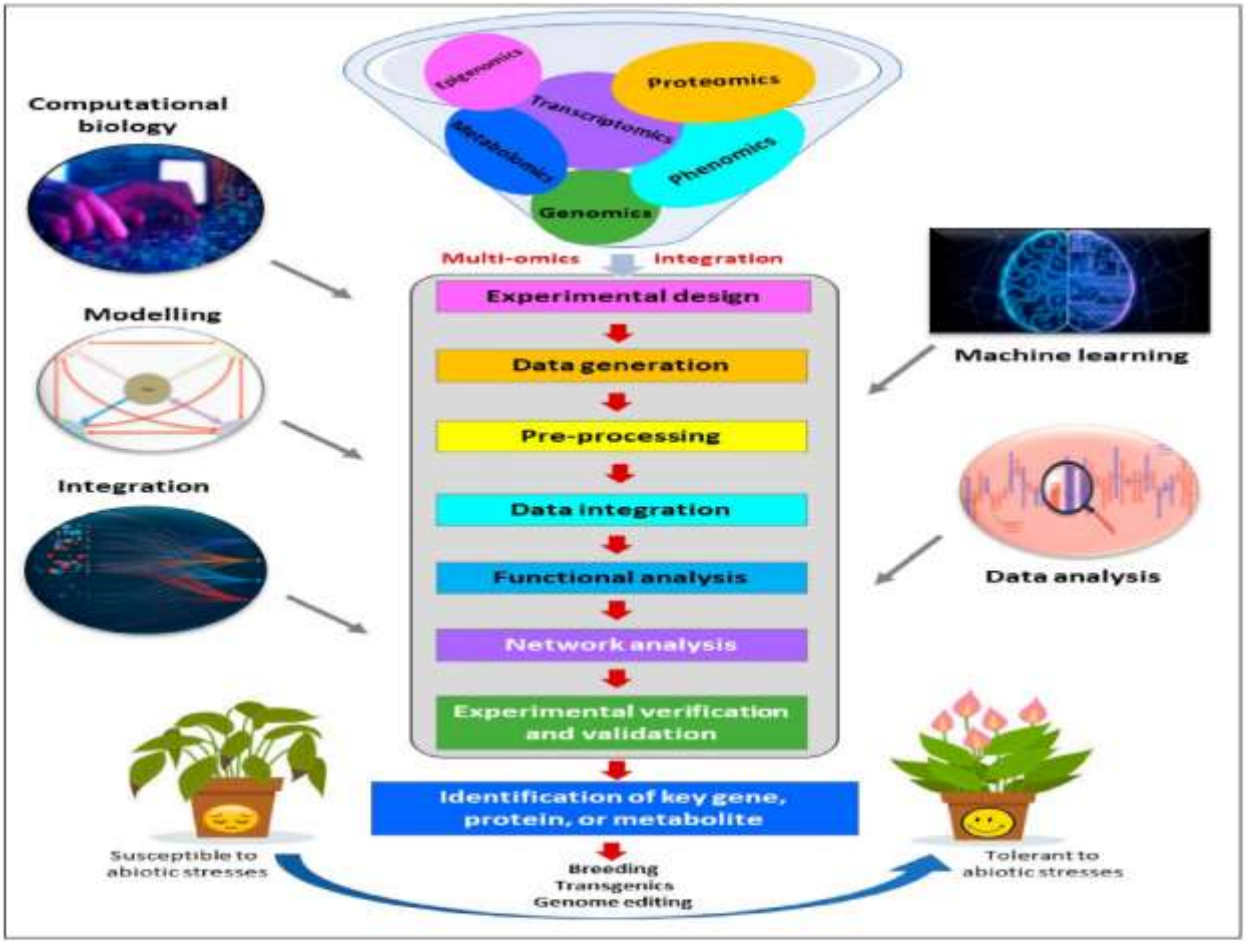

Figure 3. Multi-omics integration framework for dissecting heavy metal stress responses in *Amaranthus spp.* Genomics identifies candidate genes and genetic variants (QTLs, SNPs). Transcriptomics reveals differential gene expression under stress conditions. Proteomics provides insights into protein abundance and post-translational modifications (PTMs), while metabolomics captures stress-induced metabolic reprogramming. Integration of these datasets through systems biology approaches enables the construction of regulatory networks and identification of key biomarkers for stress tolerance

While there has been an explosion in the use of omic technologies to study amaranth, most areas of research are still developing, with many high-throughput techniques developing, many of which are currently underdeveloped in their ability to generate data (Clouse et al., 2016). Much progress has been made in developing more genomic resources, with multiple high-quality high-throughput genome assemblies for many important species like *A. hypochondriacus* (Commercial, Used for Ingredients), *A. cruentus*, and *A. palmeri* (Commonly Found in Pasture & Weeds Around The World) that allow researchers to access genome sequences of a range of important plant species through integrated databases such as the Amaranth Genomic Resource Database (AGRD) for access to Whole Genome Sequences, Single Nucleotide Polymorphisms (SNP), Simple Sequence Repeats (SSR), Transcription Factors (TF) and Micro RNAs (miRNA) (Clawson et al., 2023; Ma et al., 2021; Raiyemo et al., 2025). The use of the transcriptomic data to identify genes involved in the uptake of nutrients and water and the regulation of metabolic functions and adaptation to environmental conditions has just recently begun to occur (Escolà et al., 2026; Imadi et al., 2015). The use of the proteomics data for comparative purposes between cultivated and non-cultivated species is still the primary method for conducting proteomic research, with comparative proteomics studies demonstrating differences between levels of abundance for seed storage protein types and ongoing work demonstrating the active role of PTMs (i.e., lysine acetylation) in generating proteoform diversity that will affect enzyme function and provide stress tolerance capacity for plants (Barba de la Rosa et al., 2026; Bojórquez-Velázquez et al., 2024; Nyonje et al., 2025). By using proton-magnetic-resonance techniques to conduct metabolomic analyses, it has been possible to demonstrate that different amaranths have different metabolite profiles (e.g., trehalose and glutamine) and that these metabolite profiles differ between different amaranths grown under different growth environments, which may contribute to growth and adaptation to stress (Liu et al., 2021) (Figure 4). Despite this progress, the use of proteomics and metabolomics (as with many areas of omic technology) to gain a better understanding of plant growth processes remains to be fully explored.

Phytoremediation Potential of Amaranthus spp.

Amaranthus spp. offers great potential for phytoremediation to grow rapidly and produce large amounts of biomass (Huang et al., 2024; Yap et al., 2022). Amaranthus also has a high level of adaptability ecologically and an impressive tolerance to many abiotic environmental stressors, which enables contributions of their effective uptake and accumulation of metals (Alsherif et al., 2024; Nkuna et al., 2025). Amaranthus is therefore well-suited for use in areas that are contaminated or that have marginal soil. The efficiency of Amaranthus as a phytoremediation tool will depend upon biochemical and physiological mechanisms occurring at the molecular level, which provide the various processes that contribute to the bioavailability of all the metals (Sharma et al., 2023). The mechanisms of metal ion uptake from the rhizosphere, translocation and accumulation through the xylem, and detoxification are all processes based on the relationship between specific protein transporters associated with root tissue and overall phytoremediation performance of Amaranthus (Hussain et al., 2024). Root transporter proteins such as HMA, NRAMP, and ZIP transporters facilitate the uptake of the metal ions in the rhizosphere, while long-distance transport occurs via xylem through a xylem system (Chen et al., 2023). After metals are taken up, they are then chelated by phytochelatins and metallothioneins and then compartmentalized to vacuoles for sequestration and detoxification to less toxic forms of the metals (Sethi, 2023). These mechanisms work together to provide metal tolerance and accumulation potential in Amaranthus, both of which determine overall phytoremediation effectiveness (Huang et al., 2024). Amaranthus has the potential to perform numerous tasks for remediation and sustainable production based on the species and environmental conditions via diverse modes of phytoremediation, such as phytoextraction and phytostabilization (Huang et al., 2024). The dual-purpose nature of Amaranthus (as both a food crop and phytoremediation tool) creates additional issues related to food safety—specifically, the possible accumulation of heavy metals in edible tissues (Macías-Naranjo et al., 2026). Genotype selection and proper management practices will be critical to achieve an ideal combination between remediation efficiency and safe agricultural use.

The development of new omics technologies provides a unique opportunity to enhance the phytoremediation potential of the Amaranthus species. Integrative analyses of an organism's genome, transcriptome, proteome, and metabolome will provide information regarding key genes, regulatory networks, and metabolic pathways relevant to the uptake and tolerance of metals (Chawla et al., 2024). These data can be used for marker-assisted selection, genomic selection, and genome editing to develop improved cultivars with optimized capacities for phytoremediation. Furthermore, combining omics-based breeding with artificial intelligence and predictive modeling will expedite the identification of superior genotypes under a variety of environmental conditions. Overall, the Amaranthus species has enormous potential to serve both as a sustainable crop and to remediate contaminated environments. The strategic integration of molecular information with agronomic practices may provide for the efficient utilization of Amaranthus in phytoremediation programs while minimizing risk (Figure 5).

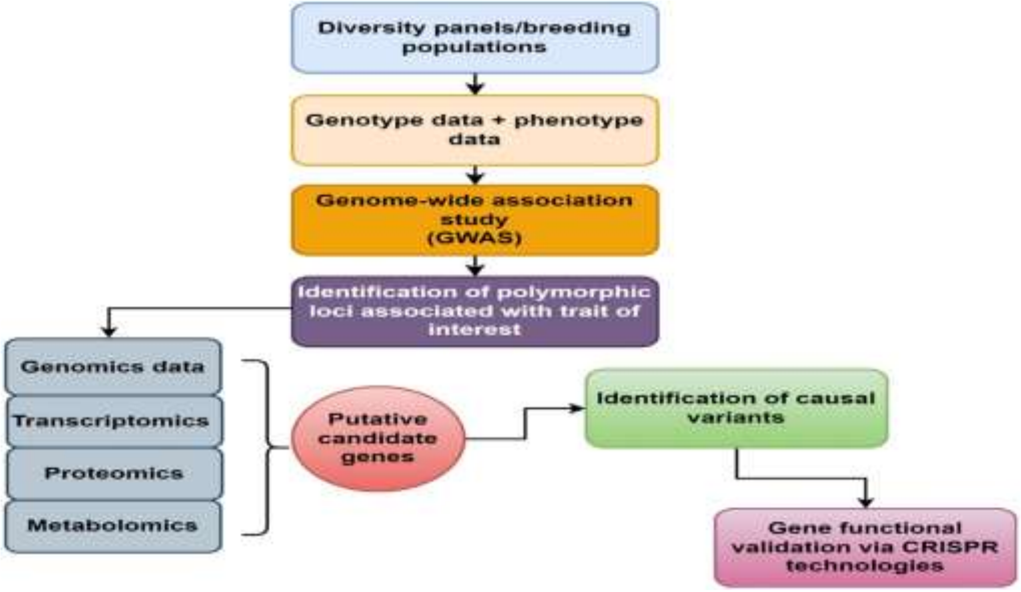

Figure 4. Translational pipeline from omics discovery to development of stress-resilient *Amaranthus* cultivars. Candidate genes identified through multi-omics analyses are validated via functional genomics approaches. These genes are incorporated into breeding programs using marker-assisted selection (MAS), genomic selection

(GS), and CRISPR/Cas-mediated genome editing. Improved lines are evaluated under controlled and field conditions to develop high-yielding, nutritionally enhanced, and heavy metal-tolerant cultivars.

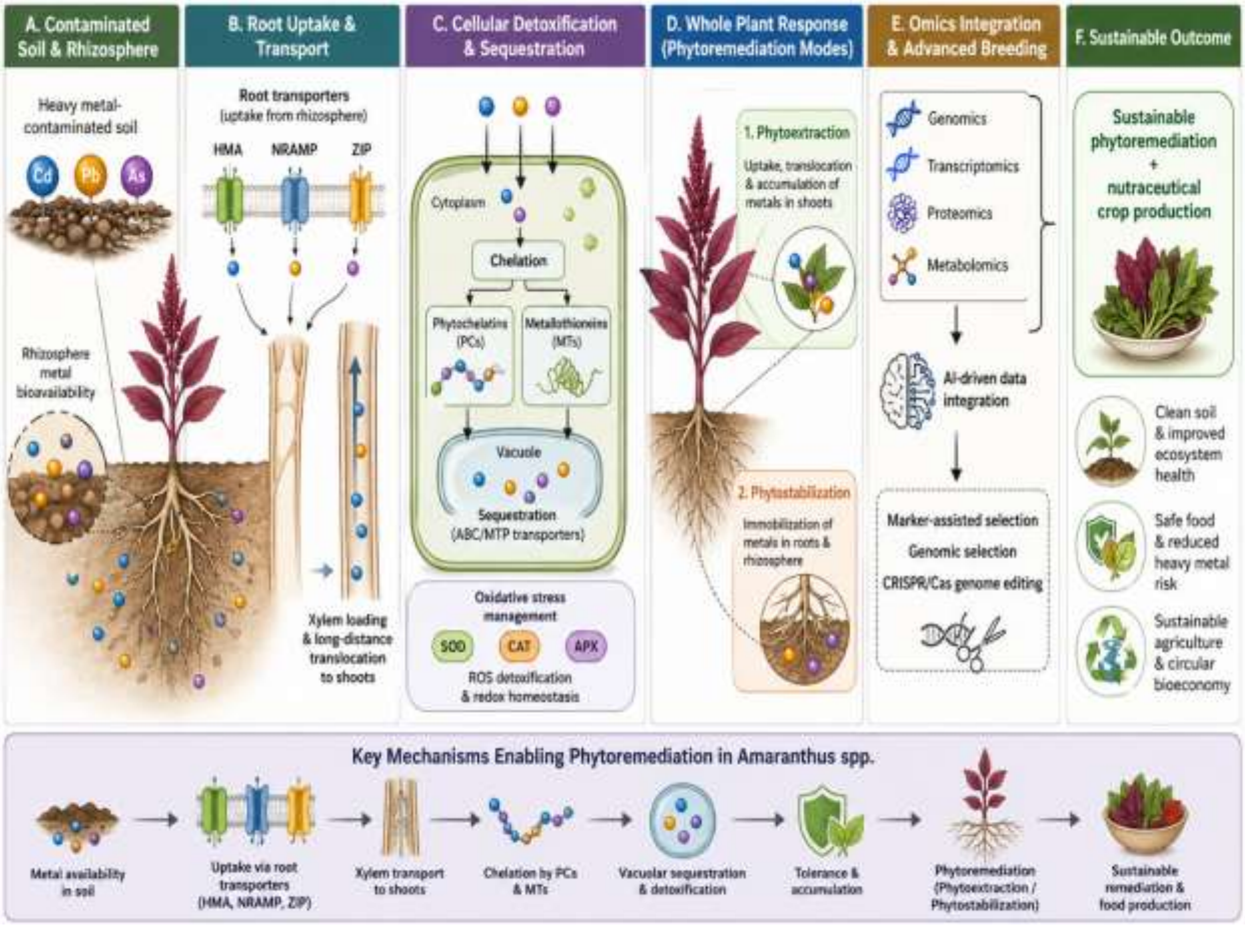

Figure 5. Conceptual framework illustrating phytoremediation potential of *Amaranthus spp.* under heavy metal stress. The diagram integrates rhizospheric metal uptake via transporter proteins (HMA, NRAMP, ZIP), xylem-mediated translocation, intracellular detoxification through chelation (phytochelatins and metallothioneins), and vacuolar sequestration. These processes underpin phytoremediation strategies such as phytoextraction and phytostabilization. Integration of multi-omics approaches with artificial intelligence and genome editing enables the development of improved cultivars for sustainable soil remediation and safe agricultural production.

Challenges and Strategic Future Directions

While great strides have been made in the field, the use of omics technologies in improving amaranth faces many challenges. The low level of genetic diversity among cultivated species restricts breeding options and limits their ability to adapt to environmental stresses (Salgotra and Chauhan, 2023). In addition, the use of transformation technologies is still in its infancy, making it very difficult to use genome editing tools such as CRISPR or CAS (Clustered Regularly Interspaced Short Palindromic Repeats) systems (Ganger et al., 2023).

At the same time, another challenge associated with the use of omics-based technology is that multi-omic datasets cannot be easily integrated or interpreted. When investigating multiple omic levels, the complexity and amount of data generated mean that advanced computational tools and bioinformatics, which are still limited for many of the current studies, will need to be developed (Figure 6). Furthermore, the lack of a standardized database or analytical pipelines for Amaranthus species has created a significant barrier to data sharing and comparative analysis.

Table 2. Major Bottlenecks and Strategic Resolutions for Multi-Omics and Genome Editing–Driven Heavy Metal Remediation in *Amaranthus*

Challenge	**Molecular / Technical Implication**	**Proposed Strategic Resolution**	**Expected Outcome**
Low genetic diversity in cultivated *Amaranthus*	Restricted allelic variation for metal transporter genes (e.g., *NRAMP*, *HMA*, *MTP*),	Systematic germplasm exploration including wild relatives, landraces, and gene bank resources;	Expanded allele pool for metal tolerance, enhanced breeding resolution

	limiting marker-assisted and genomic selection	implementation of core collection for GWAS	
Poor transformation and regeneration efficiency	Inefficient *Agrobacterium*- or biolistic-mediated gene transfer; low CRISPR-Cas9 editing frequency in recalcitrant genotypes	Optimization of tissue culture protocols (hormonal regimes, explant types); development of genotype-independent transformation methods; use of viral vectors or nanoparticle-mediated delivery	High-efficiency genome editing for multiplex trait stacking
High-dimensional multi-omics data complexity	Fragmented integration of genomics, transcriptomics, proteomics, and metabolomics; difficulty in identifying causal regulatory hubs	Implementation of AI/ML pipelines (random forest, deep learning, network inference algorithms) for data integration and predictive modeling	System-level understanding of metal chelation, vacuolar sequestration, and ROS homeostasis networks
Regulatory and biosafety barriers	Restricted field release and commercial deployment of genome-edited metal-tolerant and biofortified *Amaranthus* cultivars	Harmonized policy frameworks for CRISPR-edited crops (SDN-1 classification); stakeholder engagement; evidence-based biosafety assessment	Accelerated translation from lab to field; public and market acceptance

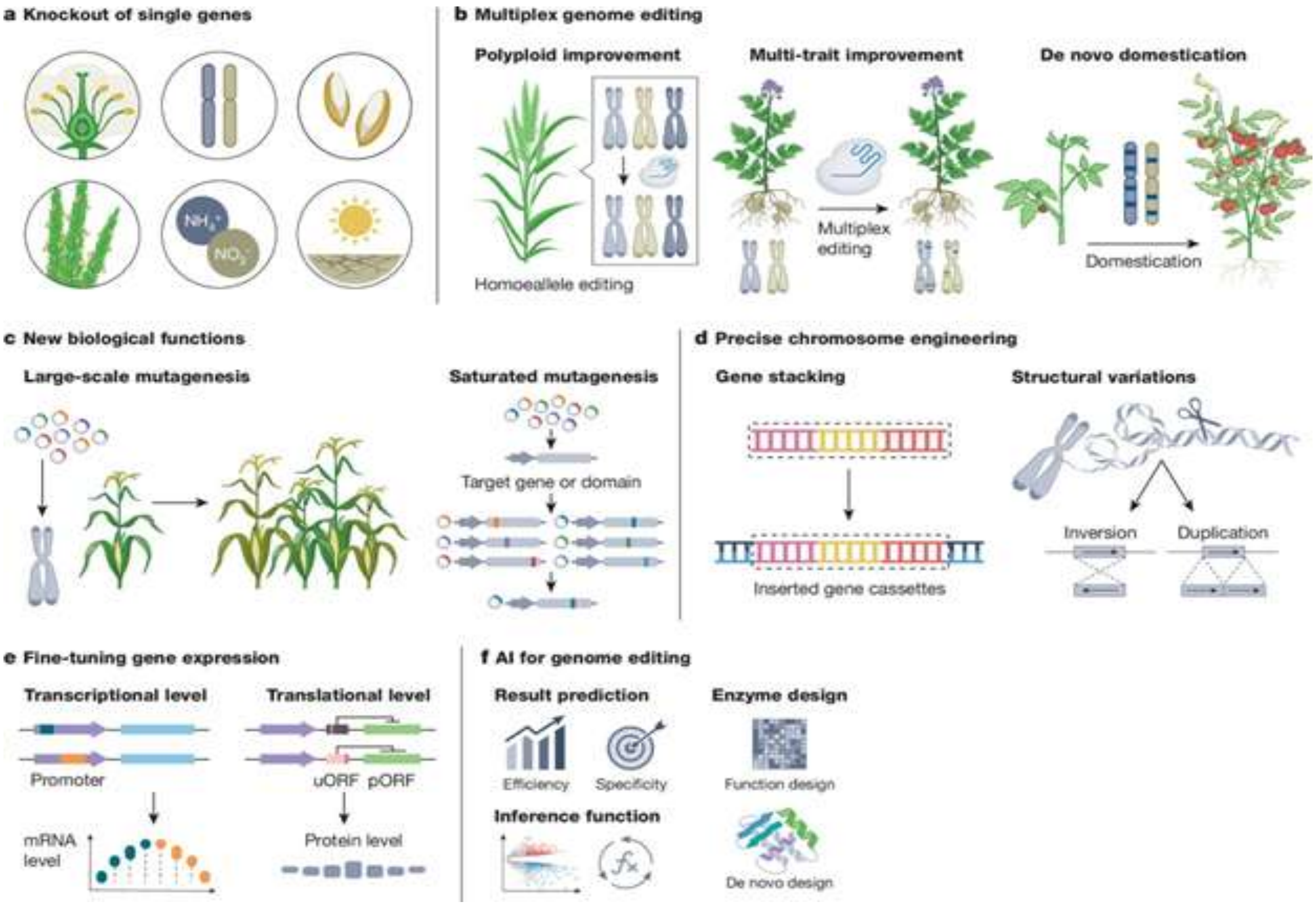

Figure 6. Overview of advanced plant genome engineering approaches: (a-b) single gene knockout and multiplex genome editing for polyploid and multi-trait improvement; (c-d) creation of new biological functions via large-scale mutagenesis and precise chromosome engineering through inversions/duplications; (e-f) fine-tuning of gene expression at transcriptional and translational levels, integrated with AI-driven prediction and de novo design of editing systems.

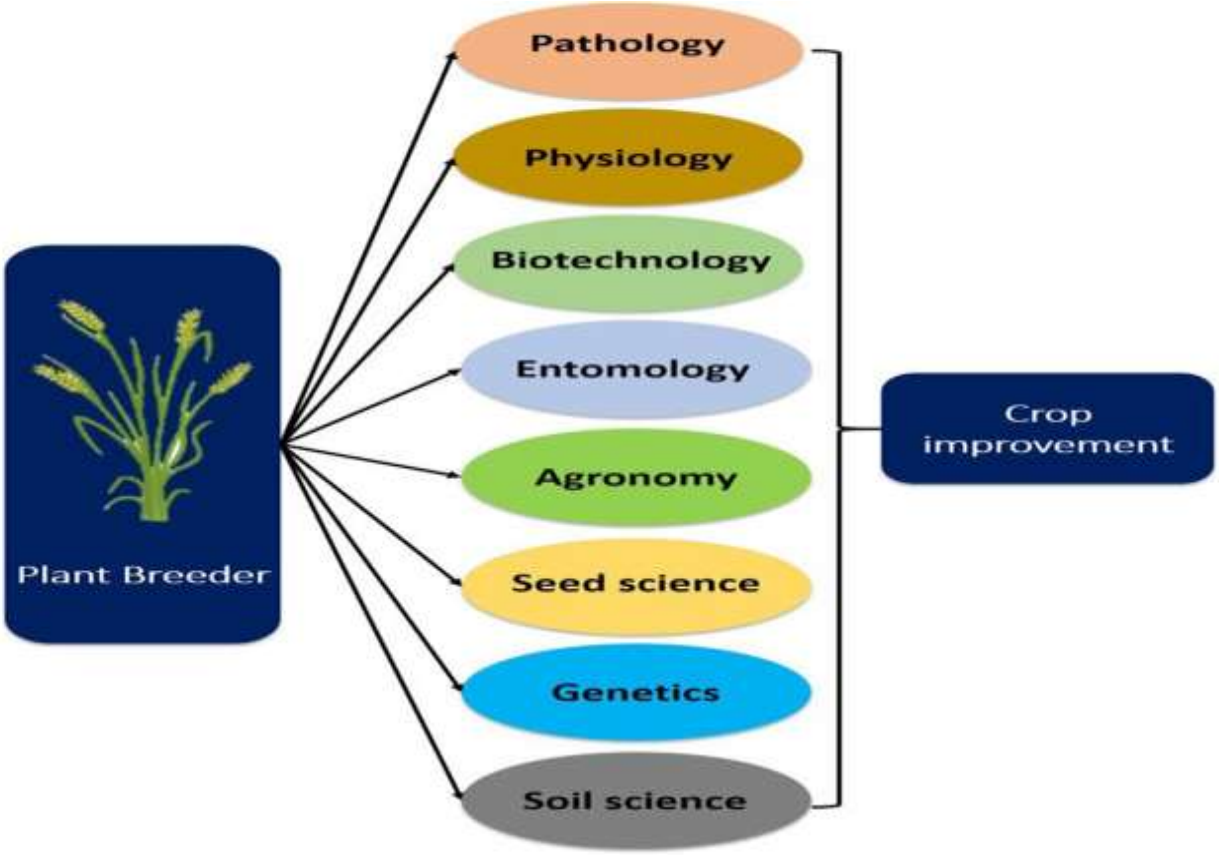

Figure 7. Multi-omics and genome editing-enabled breeding framework for heavy metal (Cd, Pb, As) remediation in amaranth, integrating transcriptomics, proteomics, metabolomics, CRISPR, and AI analytics with soil remediation and stress physiology to develop resilient, metal-tolerant, and nutraceutical-rich cultivars.

Future Perspectives

Future research efforts should include creating improved male shoot sterility methods, improving both yield and nutrition at the same time through targeted introgression of germplasm and optimizing CRISPR protocols (Fang et al., 1996; Gudu and Gupta, 1988). These should also involve developing effective and stable transformation methods to allow for functional genomics and trait engineering; constructing comprehensive amaranth species-specific pan-genomes, including genomics, proteomics, metabolomics and phenomics, as well as integrating systems biology and machine learning (ML) algorithms to predict stress-responsive networks and candidate genes for breeding programs (Farooq and Siddique, 2022; Pal et al., 2013; Sandhu et al., 2025).

Relevant to the breeding of new varieties using integrating various types of data, integrating epigenomics data so it is possible to learn how the genome adapts to or is influenced by environmental stress, and facilitating the development of best practices for implementing agricultural robots to assist in large-scale production (Figure 7) (Balabantaray et al., 2024; Lancíková et al., 2023; Vollmer et al., 2025).

Conclusion

The application of omics technologies is changing the way we look at plant stress biology and improving the crops that we produce. For *Amaranthus* spp. There are a large number of established genomic resources, and the use of proteomics and metabolomics is beginning to yield valuable functional information. However, without a consolidated approach to multi-omics integration and functional validation, the full use of this data remains untapped. The most promising strategy to address breeding challenges and utilize genome editing opportunities is through the development of a unified systems biology framework. This will provide the necessary tools/resources required to expedite the creation of resilient, nutrient-rich *Amaranthus* varieties, which have the potential to be fundamental crops contributing toward creating a sustainable and food-secure future.

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Statements and Declarations

Authors' contributions

LI: Conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft, writing – review and editing, visualization (including tables and figures), and project administration. SA and QA: Contributed through general discussion and review of the final manuscript.

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