

Review

Proposed Epigenetic Regulatory Frameworks at the Plant–Microbiome Interface Under Cadmium Stress

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Abstract

Cadmium (Cd) contamination of agricultural soils threatens crop productivity and food safety by disrupting physiological and molecular processes in plants. Increasing evidence indicates that epigenetic regulation, including DNA methylation, histone modifications, and emerging epitranscriptomic marks such as RNA methylation, plays a crucial role in coordinating plant responses to Cd stress. In parallel, plant-associated microbiomes have emerged as influential modulators of metal uptake, antioxidant capacity, hormone signaling, and stress resilience. Yet the mechanisms by which microbiome-derived signals intersect with host chromatin and transcriptome regulation under Cd exposure remain poorly understood. This review synthesizes current knowledge on plant epigenetic responses to Cd stress and critically examines how microbial metabolites, phytohormones, and redox-active compounds shape plant regulatory networks. Network-based ecological studies reveal that increased microbial community complexity and cooperative interactions are consistently associated with reduced Cd accumulation and enhanced plant performance, suggesting that microbial organization itself may represent an additional regulatory layer influencing plant responses. Despite compelling conceptual links, direct experimental evidence connecting microbiome signals to stable epigenetic or epitranscriptomic reprogramming under Cd stress remains limited. To date, only limited experimental studies have demonstrated causal relationships between microbial cues and host DNA or RNA methylation dynamics in Cd-exposed plants, highlighting clear mechanistic potential while also underscoring remaining knowledge gaps. By integrating physiological, ecological, and chromatin-level perspectives, this review identifies key unanswered questions and outlines future research directions to establish causal links between microbial community dynamics, epigenetic regulation, and long-term Cd stress adaptation in plants.

Keywords: cadmium stress; plant epigenetics; rhizosphere microbiome; DNA methylation; microbiome–plant interactions; stress adaptation



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1. Introduction

Cadmium (Cd) is one of the most toxic and persistent metal pollutants affecting agricultural soils worldwide. Unlike essential mineral nutrients, Cd has no known biological function in plants and primarily enters terrestrial ecosystems through anthropogenic activities, including mining, metal processing, urban waste disposal, and the long-term use of phosphate fertilizers [1,2]. Due to its chemical similarity to essential divalent cations, including Zn^{2+} and Ca^{2+} , Cd is readily taken up by plant roots and can be translocated to aerial tissues. As a result, crop plants represent a major entry pathway of Cd into the food chain, posing serious risks to food safety and human health [3,4].

Exposure to Cd disrupts multiple physiological and molecular processes in plants. Cadmium stress interferes with nutrient uptake, reduces photosynthetic efficiency, induces oxidative damage, and perturbs hormonal and redox signaling networks [5,6]. To cope with these effects, plants activate multiple defense mechanisms, including Cd²⁺ chelation, vesicular sequestration, and enhanced antioxidant defenses [7]. Although these responses mitigate Cd toxicity, growth inhibition and yield penalties are frequently observed under prolonged exposure in contaminated soils.

In recent years, epigenetic regulation has emerged as an important layer controlling plant responses to Cd stress. Changes in DNA methylation, histone modifications, chromatin structure, and small-RNA activity have been reported to influence gene expression patterns and contribute to stress adaptation processes [8,9]. Genome-wide and gene-specific analyses in rice, wheat, and Arabidopsis have demonstrated that Cd exposure induces locus-specific as well as global alterations in DNA methylation, influencing genes involved in metal transport, detoxification, and stress signaling pathways [10–12]. Importantly, some Cd-induced epigenetic modifications have been reported to persist across generations or to contribute to transgenerational epigenetic variation, suggesting a potential role in stress memory and heritable adaptation [13,14].

At the same time, increasing attention has been given to how Cd stress reshapes rhizosphere microbial communities and how plant-associated microbiota, in turn, influence plant performance under metal stress [15,16]. Numerous studies indicate that beneficial microbes can reduce Cd accumulation or restrict its translocation, enhance antioxidant defenses, and improve plant growth under contaminated conditions [17–19].

Despite these advances, epigenetic regulation and microbiome-mediated Cd tolerance have generally been addressed in parallel rather than in an integrated framework. Epigenetic research has mainly focused on plant-intrinsic mechanisms, often under controlled or sterile conditions, whereas microbiome studies have emphasized physiological, biochemical, and agronomic outcomes without explicitly addressing chromatin-level regulation in the host plant [9,18]. As a result, direct experimental evidence linking microbial signals to epigenetic reprogramming in plants exposed to Cd remains limited. Nevertheless, growing evidence indicates that microbial-derived phytohormones and redox-active metabolites modulate host hormonal balance and antioxidant systems [20–22], suggesting potential indirect links to chromatin-level regulation that remain to be experimentally verified.

Plant epigenetic research and plant–microbiome studies have expanded rapidly in recent years, yet their conceptual integration remains limited. While epigenetic analyses of cadmium stress are predominantly performed under sterile or simplified experimental systems, microbiome-based studies operate in ecologically complex environments but largely overlook chromatin-level regulation. This disconnect highlights a significant gap in interpreting how microbial cues influence transcriptional plasticity and stress memory under heavy metal stress.

Integrating epigenetic regulation into the plant–microbiome framework therefore represents an important conceptual challenge. Microbial signals that alter hormonal balance, redox status, and metabolic fluxes may indirectly shape chromatin states, thereby influencing transcriptional plasticity, stress memory, and long-term adaptation to Cd-contaminated environments. However, a unified framework connecting microbial activity to defined epigenetic modifications under Cd stress is still lacking.

Accordingly, this review synthesizes current knowledge on plant epigenetic responses to cadmium toxicity and microbiome-mediated modulation of plant stress physiology. By bringing these two research areas together, the review aims to identify emerging molecular connections, highlight critical knowledge gaps, and provide a conceptual basis for future

studies exploring how microbial signals intersect with epigenetic regulation to shape plant adaptation under Cd stress.

2. Cadmium Stress-Induced Epigenetic Regulation in Plants

Cadmium exposure triggers significant transcriptional changes in plants. Transcription factors represent a key regulatory layer in Cd stress responses, with several families including WRKY, ERF, MYB, bHLH, and bZIP reported to play central roles in mediating plant resistance to Cd stress [23]. Transcriptomic evidence from the Cd hyperaccumulator *Phytolacca acinosa* shows that exogenous ABA affects the expression of metal transport, chelation, defense, and hormone-related genes under Cd stress [24]. However, transcriptional regulation alone may not fully account for the stability, reversibility, and potential heritability of Cd-induced stress responses.

Accumulating evidence indicates that epigenetic regulation plays a key role in modulating both immediate stress responses and longer-term adaptive processes under Cd exposure. These regulatory processes include dynamic changes in DNA methylation, RNA methylation, histone modifications, chromatin organization, and small-RNA-mediated pathways, which influence gene expression under Cd stress conditions [14,25].

2.1. DNA Methylation Dynamics Under Cadmium Stress

DNA methylation is a conserved epigenetic mechanism in plants that involves the addition of methyl groups to cytosine residues in DNA by DNA methylases [26]. This modification regulates gene expression and contributes to the reprogramming of transcription in response to environmental stresses [27]. In particular, stress-induced changes in DNA methylation may contribute to longer-term stress memory in plants [28].

Within the context of heavy metal toxicity, accumulating evidence indicates that DNA methylation participates in plant responses to Cd stress, contributing to the maintenance of genome integrity under Cd exposure [29] and influencing transcriptional regulation through stress-associated changes in gene methylation patterns [30]. Genome-wide single-base resolution analyses in rice demonstrated that Cd exposure induces widespread alterations in CG, CHG, and CHH methylation patterns, with more hypermethylated than hypomethylated regions detected across upstream, gene body, and downstream regions [10]. These differentially methylated regions were associated with transcriptional changes in genes involved in stress responses, metal transport, and transcriptional regulation, including *OsIRO2*, *OsPR1b*, and *Os09g02214*. Functional analyses using mutants defective in DNA methyltransferases revealed that *MET1* and *DRM2* are required to maintain appropriate expression of Cd-responsive genes, supporting a mechanistic link between DNA methylation and transcriptional regulation under Cd stress [10].

Consistent with these findings, Cd-induced DNA methylation levels increased in the Cd-hyperaccumulator *Noccaea caerulescens* Ganges, where Cd exposure led to higher CpG DNA methylation and upregulation of the DNA-methyltransferase gene *MET1*, contributing to the maintenance of genome integrity under Cd stress [29]. Gene-specific methylation analyses in wheat further demonstrated that Cd exposure alters DNA methylation and transcription of *UGT-3*, *LTP-4*, and *PIP-1*, with methylation changes correlating with gene expression related to detoxification, membrane transport, and stress responses [30]. These studies support a role for DNA methylation-mediated transcriptional control in plant responses to Cd stress.

More refined mechanistic insight comes from recent work in rice showing that Cd stress dynamically regulates CHH methylation at a miniature inverted-repeat transposable element (MITE) located in the promoter region of *OsGSTZ4*. Cd exposure triggered rapid transcriptional induction of *OsGSTZ4*, followed by siRNA accumulation and CHH

hypermethylation mediated through the RNA-directed DNA methylation (RdDM) pathway, specifically requiring *OsDRM2* and *OsRDR2* [31]. This study reveals an epigenetic feedback mechanism in which Cd-induced gene activation is subsequently modulated by siRNA-guided methylation, contributing to the regulation of transcriptional responses during Cd stress.

Importantly, Cd-induced DNA methylation changes can persist across generations. Analysis of heavy-metal-treated rice and its successive generations demonstrated that Cd exposure induces CHG hypomethylation at specific loci, and that these epigenetic modifications are heritable through both maternal and paternal germlines [32]. Progeny of stressed plants exhibited enhanced tolerance to the same stress encountered by their parents, supporting the notion that environmentally induced DNA methylation changes may contribute to the transgenerational inheritance of Cd tolerance traits.

Collectively, these studies establish DNA methylation as a dynamically relevant regulatory layer in plant responses to cadmium stress, operating at both genome-wide and locus-specific levels. By modulating the expression of stress-responsive, detoxification-related, and regulatory genes, including *OsIRO2*, *OsPR1b*, *Os09g02214*, *UGT-3*, *LTP-4*, *PIP-1*, and *OsGSTZ4*, through canonical DNA methyltransferases (*MET1*, *DRM2*) and RNA-directed DNA methylation pathways (*OsDRM2*, *OsRDR2*), DNA methylation contributes not only to immediate stress acclimation but also to longer-term adaptive potential, including transgenerational inheritance of Cd tolerance traits.

2.2. Histone Modifications and Chromatin Remodeling

Histone modifications constitute a central epigenetic mechanism regulating gene expression in response to abiotic stresses. Post-translational modifications of histone tails, including acetylation, methylation, phosphorylation, ubiquitination, and sumoylation, play key roles in transcriptional regulation and plant stress tolerance [33]. These chromatin changes are tightly coordinated with transcription factor activity via histone-modifying enzymes and chromatin-associated cofactors, whose activity, stability, and chromatin recruitment are themselves regulated by post-translational modifications, particularly phosphorylation [34]. Within this regulatory framework, post-translational modifications, particularly phosphorylation, function as critical modulators of histone-modifying enzymes, thereby fine-tuning transcriptional responses to environmental and developmental cues.

Consistent with this concept, Cd exposure significantly alters plant gene regulation by modifying histone marks and chromatin organization. In Pakchoi, Xiang et al. [35] reported that Cd treatment disrupts nucleolus organization, decondenses 45S rDNA chromatin, and increases transcription from the 5' external transcribed spacer (ETS) region. These structural changes were accompanied by genome-wide alterations in histone acetylation and methylation, including elevated H3K9ac, H4K5ac, and H3K9me2 levels at the 45S rDNA promoter. Site-specific DNA hypomethylation within the promoter region was also associated with activation of rDNA transcription, suggesting a mechanistic link between chromatin remodeling, epigenetic modification, and nucleolar integrity under Cd stress.

Cao et al. [36] investigated the interplay between reactive oxygen species (ROS) and histone modifications in Cd-stressed Pakchoi seedlings. Cd-induced ROS accumulation was associated with chromatin decondensation and DNA damage, whereas low concentrations of epigenetic modification inhibitors enhanced histone acetylation and attenuated cell cycle arrest. These effects were associated with coordinated regulation of histone acetyltransferase and deacetylase gene expression, and antioxidant treatment further strengthened this protective response. Notably, high concentrations of the Histone deacetylase (HDAC) inhibitor Trichostatin A (TSA) increased ROS accumulation, suggesting a bidirectional interaction between chromatin state and oxidative stress under Cd exposure.

In other plant systems, Gocek-Szczurtek et al. [37] showed that Cd exposure activates nuclear MAPKs and increases global DNA methylation (5-mC) levels, accompanied by pronounced alterations in histone modifications, including decreases in *H3K4Me2*, *H3T45Ph*, and *H4K5Ac* and increases in *H3K9Ac* and *H3K56Ac*. These changes were associated with chromatin condensation and transcriptional repression. Co-treatment with thyme oil stabilized MAPK activity, preserved chromatin organization, and prevented transcriptional silencing, highlighting its role in maintaining epigenetic stability under Cd stress.

Histone demethylases also contribute to Cd tolerance. Dong et al. [38] reported that *SIJM18* and *SIJM23* modulate Cd responses by influencing hormone synthesis pathways (BRs and ABA) and phenolic compound accumulation, whereas Li et al. [39] demonstrated that *SIJM524* enhances Cd tolerance through regulation of the glutathione–phytochelatin (*GSH-PC*) detoxification pathway and flavonoid biosynthesis. These findings highlight the developmental stage- and gene-specific roles of histone demethylases in modulating plant responses to Cd toxicity.

Despite these advances, studies on chromatin accessibility and long-range regulatory interactions under Cd stress remain scarce. Research in *Arabidopsis thaliana* indicates that organ-specific accessible chromatin regions are strongly associated with active histone marks such as *H3K4me3* at promoter sites, whereas many organ-unique accessible regions are located in distant intergenic regions and enriched for transcription factor binding motifs [40]. However, it remains unclear how Cd exposure affects these chromatin landscapes and whether long-range interactions contribute to tissue-specific stress responses, representing a critical gap for future investigation.

Cd stress induces dynamic histone modifications and chromatin remodeling, involving ROS signaling, MAPK activation, and developmental regulation. These epigenetic changes provide plants with flexible mechanisms to modulate gene expression, maintain cellular homeostasis, and enhance tolerance to cadmium toxicity.

2.3. Non-Coding RNAs in Cadmium-Responsive Gene Regulation

Long non-coding RNAs (lncRNAs) constitute a diverse class of regulatory transcripts that play important roles in gene expression control and genome stability in plants. Although lncRNAs can function in both nuclear and cytoplasmic compartments, the majority are enriched in the nucleus and are frequently associated with chromatin, where they act as regulators of transcriptional and epigenetic states [41]. Mechanistically, plant lncRNAs function as versatile cis- and trans-acting regulators, serving as molecular scaffolds that recruit chromatin-modifying complexes and regulate gene expression at multiple levels [42]. Recent high-throughput sequencing studies have revealed that lncRNAs can directly interact with chromatin, DNA, and nuclear proteins, thereby conditioning the epigenetic environment of target genes and modulating transcriptional regulation [43].

In the context of heavy metal stress, such regulatory versatility suggests that lncRNAs may act as integrative nodes linking stress-induced signaling pathways with chromatin-level modulation of gene expression.

2.3.1. MicroRNAs and Small RNAs in Cd Stress Responses

MiRNAs are ~21-nucleotide non-coding RNAs that function as key post-transcriptional regulators of gene expression and are involved in plant responses to metal toxicity [44]. In wheat, Qiu et al. [45] demonstrated that Cd exposure induces differential expression of five Cd-responsive miRNAs and their corresponding targets in both roots and leaves. Notably, miR398 was implicated in Cd-induced oxidative stress tolerance through regulation of its target gene encoding copper/zinc superoxide dismutase (CSD). Most miRNA–target

pairs exhibited complex and tissue-specific regulatory patterns, suggesting that miRNAs participate in the mediation of Cd stress responses.

Similar regulatory patterns have been reported in other crops. In maize, Gao et al. [46] showed that Cd exposure induced differential expression of six candidate miRNAs and their targets in seedling roots. Expression changes were validated by qRT-PCR across different exposure times, and in situ hybridization further confirmed the spatial expression pattern of *Zma-miR171b* under Cd stress. In rice, Ding et al. [47] identified 19 Cd-responsive miRNAs through microarray profiling, with predicted target genes encoding transcription factors and stress-related proteins. Several miRNA–target pairs exhibited negative expression correlations under Cd stress. Promoter analyses further indicated that metal stress-responsive cis-elements tended to occur more frequently in the promoter regions of Cd-responsive miRNA genes, suggesting transcriptional regulation of miRNA expression in response to Cd exposure.

Functional studies further revealed that miRNAs can act as either positive or negative regulators of Cd tolerance. Ding et al. [48] demonstrated that *miR268* is significantly induced by Cd stress in rice, leading to repression of its target gene *NRAMP3*, a metal transporter. Overexpression of *miR268* inhibited seedling growth under Cd stress and resulted in increased Cd accumulation as well as elevated hydrogen peroxide and malondialdehyde levels, indicating enhanced oxidative stress. These findings demonstrate that excessive *miR268* activity negatively affects Cd tolerance and underscore the importance of balanced miRNA regulation in determining plant sensitivity or resistance to Cd stress.

Beyond canonical miRNAs, broader small-RNA populations also contribute to Cd responses. Using small-RNA and degradome sequencing, Ma et al. [49] identified hundreds of sRNAs responsive to excessive Cd and Cu treatments, including DCL1-dependent and DCL2/3/4-dependent species. Several sRNAs originated from rRNA, tRNA, and Trans-acting siRNA (TAS) loci, and many were responsive to both Cu and Cd exposure, suggesting interactions between metal stress signaling pathways. Functional network analyses further indicated that sRNA–target interactions were associated with hormone–stress signaling pathways and reproductive processes, highlighting the regulatory diversity of sRNA-guided mechanisms under heavy metal stress.

Genotype- and tissue-specific regulation of small RNAs has also been linked to Cd accumulation traits. Liu et al. [50] compared high- and low-Cd-accumulating wheat cultivars and identified distinct small RNA expression profiles in roots and leaves following Cd treatment. Several differentially expressed miRNAs and their predicted targets were associated with cultivar-specific differences in Cd accumulation, suggesting a role for miRNA-mediated regulation in Cd accumulation processes. These miRNAs were proposed as potential biomarkers for screening low-Cd-accumulating wheat varieties.

2.3.2. Long Non-Coding RNAs in Cadmium-Responsive Transcriptional and Epigenetic Regulation

Beyond post-transcriptional regulation, lncRNAs may influence gene expression by associating with neighboring genes and modulating miRNA activity, thereby contributing to gene regulation under Cd stress. Strand-specific RNA sequencing in rapeseed revealed more than 5000 lncRNAs, among which 301 were responsive to Cd exposure [51]. Many Cd-responsive lncRNAs were associated with neighboring protein-coding genes involved in Cd uptake, translocation, and stress responses, suggesting possible cis-related regulatory effects. Importantly, some lncRNAs were identified as precursors of known miRNAs, while others functioned as endogenous target mimics (eTMs) capable of sequestering miRNAs. These findings suggest an interaction between lncRNAs and miRNAs under Cd stress.

Recent studies have provided functional validation of lncRNA-mediated regulation in Cd accumulation and related stress responses. In sweet sorghum, Lin et al. [52] identi-

fied Cd-responsive lncRNAs and investigated their putative cis- and trans-target genes, including genes involved in cell wall metabolism and metal chelation. Functional assays in protoplasts demonstrated that overexpression of specific lncRNAs upregulated their corresponding cis-target genes, such as SbYS1, which encodes a Cd chelate transporter. These findings suggest a positive regulatory role of certain lncRNAs in Cd accumulation and translocation. Similarly, in wheat, Zhu et al. [53] identified 10,044 novel lncRNAs in roots under Cd stress, including 69 cis-acting lncRNA–target pairs affecting the expression of genes involved in Cd transport and detoxification, photosynthesis, and antioxidant defense. Notably, overexpression of *lncRNA37228*, targeting a photosystem II protein D1 gene, enhanced Cd resistance in Arabidopsis, providing functional evidence for the regulatory role of lncRNAs in heavy metal stress responses.

Collectively, non-coding-RNA-mediated regulatory pathways appear to operate in close coordination with DNA methylation dynamics and histone modifications to fine-tune gene expression under cadmium stress. Small RNAs can indirectly influence chromatin states by modulating the expression of epigenetic regulators and stress-responsive transcription factors, thereby interfacing with DNA methylation- and histone-based control mechanisms described in Sections 2.1 and 2.2. In parallel, accumulating evidence suggests that long non-coding RNAs contribute more directly to transcriptional and epigenetic regulation by acting as cis- or trans-regulatory elements, including molecular scaffolds or decoys, that influence the expression of neighboring genes and stress-responsive pathways at Cd-associated loci. Together, these interconnected regulatory layers form a multilayered network integrating transcriptional, post-transcriptional, and epigenetic control, thereby enhancing the capacity of plants to adapt to cadmium toxicity.

2.4. Epigenetic Stress Memory and Transgenerational Effects

An important yet still relatively underexplored dimension of Cd toxicity in plants concerns the potential establishment of epigenetic stress memory. Stress memory refers to the capacity of plants to retain information from prior stress exposure and to adjust subsequent responses either within the same generation or across generations, potentially involving epigenetic mechanisms [28]. In this review, the term “epigenetic stress memory” is used as a conceptual framework encompassing somatic, intergenerational, and transgenerational effects. In contrast, “transgenerational inheritance” is applied more specifically to situations in which stress-associated epigenetic modifications persist beyond the directly exposed generation and are transmitted to progeny, even without continued exposure to the original stress.

Mechanistically, processes such as DNA methylation, histone modifications, chromatin remodeling, and small-RNA-mediated pathways have been implicated in shaping plant stress adaptation and may contribute to memory-like effects [54,55]. Compared with other abiotic stresses, including drought and salinity, direct experimental evidence for stable epigenetic memory under Cd exposure remains limited. Nevertheless, available studies suggest that Cd stress may induce relatively stable epigenetic and transcriptional alterations, some of which may extend beyond the immediate stress period. Further research is required to determine the stability, reversibility, and potential heritability of these modifications.

In rice, Cong et al. [32] demonstrated that exposure to heavy metals, including Cd, induced locus-specific alterations in DNA methylation, predominantly manifested as CHG hypomethylation in both transposable elements and protein-coding genes. These CHG-demethylated states were transmitted through both maternal and paternal germlines and persisted for at least three successive generations. Importantly, progeny of stressed plants exhibited enhanced tolerance to the same stress conditions experienced by their progenitors, suggesting a potential association between heritable DNA methylation changes and stress-

adaptive phenotypic responses. Cd exposure was also accompanied by altered expression of genes encoding DNA methyltransferases, DNA glycosylases, and the SWI/SNF chromatin remodeling factor *DDM1*, indicating that core epigenetic regulators are likely involved in stress-associated epigenetic modifications linked to memory-like responses.

Evidence for transgenerational-plasticity-associated transcriptional memory in response to Cd exposure has also been reported in *Thlaspi arvense*. Li et al. [56] showed that maternal Cd exposure reduced growth and reproductive performance in the parental generation, whereas offspring maintained elevated superoxide dismutase (SOD) activity even under non-stress conditions. Transcriptome analysis identified 401 transcriptional memory genes (TMGs) that retained Cd-responsive expression patterns in the second generation despite the absence of Cd exposure. These TMGs were primarily associated with oxidative stress responses, cell wall biogenesis, and abscisic acid signaling pathways. Weighted gene co-expression network analysis further revealed that modules correlated with SOD activity were enriched in TMGs, and the SOD-encoding gene *CSD2* was located within one such module. Several TMGs co-expressed with *CSD2* were identified as hub genes, suggesting that transcriptional memory may contribute to the observed transgenerational plasticity under Cd stress. The major epigenetic, transcriptional, and non-coding-RNA-mediated responses to Cd stress reported across plant species are summarized in Table 1.

Table 1. Epigenetic regulatory mechanisms underlying plant responses to Cd stress.

Biological System	Epigenetic Regulatory Mechanism	Experimental/Analytical Approach	Mechanistic Insights	Physiological/Agronomic Outcomes	Proposed Research Limitations *	Reference
<i>Oryza sativa</i>	DNA methylation (CG, CHG, CHH contexts)	Whole-genome bisulfite sequencing (WGBS); RNA sequencing (RNA-seq); mutant analysis (<i>met1</i> , <i>drm2</i>); 5-azacytidine treatment	2320 differentially methylated regions (DMRs); 2092 methylation-associated genes altered; hypermethylation predominance; reduced expression of <i>OsIRO2</i> , <i>OsPRIb</i> , <i>Os09g02214</i> in <i>drm2</i>	DNA demethylation promoted seedling growth but increased Cd accumulation	Temporal dynamics and multigenerational stability not examined	[10]
<i>Nocca caerulea</i> (Ganges) vs. <i>Arabidopsis thaliana</i>	DNA methylation-mediated genome integrity regulation	Alkaline comet assay; methyl-sensitive comet assay; qRT-PCR	Increased CpG methylation and <i>MET1</i> expression in hyperaccumulator; reduced oxidative damage	Genome protection associated with Cd tolerance	Functional causality between methylation and tolerance not directly validated	[29]
<i>Triticum aestivum</i>	Gene-specific DNA methylation	Quantitative analysis of DNA methylation using amplification polymorphism (qAMP); qRT-PCR	Dose-dependent methylation changes in <i>UGT-3</i> , <i>LTP-4</i> , <i>PIP-1</i> correlated with transcription	Tissue-specific Cd tolerance responses	Genome-wide methylation landscape not assessed	[30]
<i>Oryza sativa</i>	RNA-directed DNA methylation (RdDM)	Transgenic overexpression; CHH methylation analysis; small-RNA detection; promoter deletion assays	Cd induced early <i>OsGSTZ4</i> activation followed by CHH hypermethylation via 24-nt small RNAs and <i>OsDRM2</i>	Enhanced Cd detoxification and root Cd retention	Long-term epigenetic persistence under field conditions unknown	[31]
<i>Oryza sativa</i> (S0–S3 generations)	Transgenerational CHG hypomethylation	Gel-blot methylation assay; reverse transcription PCR (RT-PCR); multigenerational phenotyping	Stress-induced CHG hypomethylation inherited via maternal and paternal lines; altered DNA methyltransferase and <i>DDM1</i> expression	Progeny exhibited enhanced Cd tolerance	Underlying chromatin context and reversibility not clarified	[32]
<i>Brassica rapa</i> (Pakchoi)	Histone acetylation and methylation at 45S rDNA	Chromatin immunoprecipitation (ChIP); DNA methylation assay; cytological analysis	Increased H3K9ac (histone H3 lysine 9 acetylation), H4K5ac, H3K9me2; promoter hypomethylation	Nucleolar reorganization and transcriptional modulation	Genome-wide histone profiling lacking	[35]

Table 1. Cont.

Biological System	Epigenetic Regulatory Mechanism	Experimental/Analytical Approach	Mechanistic Insights	Physiological/Agronomic Outcomes	Proposed Research Limitations *	Reference
<i>Brassica rapa</i> (Pakchoi)	Histone acetylation modulation via inhibitors	Epigenetic inhibitor treatments (5-AC, TSA, etc.); ROS assays; chromatin analysis	Increased histone acetylation attenuated Cd-induced ROS accumulation and DNA damage	Improved Cd tolerance through ROS–epigenetic interaction	Specific gene targets of acetylation not identified	[36]
<i>Vicia faba</i>	MAPK-associated DNA methylation and histone modification	MAPK activation assay; global 5-mC quantification; histone mark analysis	Cd doubled global 5-mC; altered H3K4Me2, H3K9Ac, H3K56Ac; thyme oil stabilized chromatin	Prevention of chromatin compaction and transcriptional repression	Stress duration limited to acute exposure	[37]
<i>Solanum lycopersicum</i>	Histone demethylases (SIJM18, SIJM23)	Gene expression analysis; transgenic overexpression; GUS staining; hormone quantification	Differential modulation of BR and ABA pathways; stage-specific Cd response	Early sensitivity but later enhanced tolerance	Direct chromatin targets not fully mapped	[38]
<i>Solanum lycopersicum</i>	Histone demethylase (SIJM524)	Transgenic overexpression; flavonoid quantification; gene expression analysis	Upregulation of glutathione–phytochelatin pathway and flavonoid biosynthesis	Adult-stage Cd tolerance enhancement	Stage-dependent regulation mechanism unclear	[39]
<i>Arabidopsis thaliana</i>	Chromatin accessibility	INTACT–ATAC sequencing (ATAC-seq)	41,419 accessible sites; enrichment of H3K4me3 in promoters; distal regulatory elements identified	Organ-specific transcriptional regulation	Cd-specific chromatin remodeling not directly validated	[40]
<i>Triticum aestivum</i>	miRNA-mediated regulation (<i>miR398</i>)	qRT-PCR; target validation	<i>miR398</i> regulates CSD affecting oxidative stress tolerance	Modulation of Cd-induced antioxidant responses	Limited number of miRNAs examined	[45]
<i>Zea mays</i>	Cd-responsive miRNAs	qRT-PCR; enzyme activity assays; in situ hybridization	Differential expression of candidate miRNAs; spatial validation of <i>Zma-miR171b</i>	Insight into Cd stress signaling in roots	Genome-wide miRNA profiling not performed	[46]
<i>Oryza sativa</i>	Cd-responsive miRNA profiling	Microarray; target prediction; expression validation	19 Cd-responsive miRNAs targeting TFs and stress proteins	Post-transcriptional regulation of Cd tolerance	Functional validation limited to subset	[47]
<i>Oryza sativa</i>	miRNA (<i>miR268</i>) regulation of metal transport	Overexpression; H ₂ O ₂ and malondialdehyde quantification	<i>miR268</i> suppresses <i>NRAMP3</i> ; increased Cd accumulation	Negative regulation of Cd tolerance	Field relevance not evaluated	[48]
<i>Arabidopsis thaliana</i>	Small-RNA (sRNA) networks	Small-RNA sequencing; degradome sequencing	DCL-dependent sRNAs responsive to Cd; TAS-derived sRNAs identified	Hormone–stress signaling integration	Functional assays for most sRNAs lacking	[49]
<i>Triticum aestivum</i>	Cd-responsive small RNAs	Small-RNA sequencing; cultivar comparison	Differential sRNAs linked to Cd accumulation differences	Potential biomarkers for low-Cd cultivars	Validation under agronomic conditions needed	[50]
<i>Brassica napus</i>	Long non-coding RNAs (lncRNAs) and eTMs	Strand-specific RNA sequencing; transient expression assays	301 Cd-responsive lncRNAs; miRNA precursor and target mimic roles	Regulation of Cd uptake and detox pathways	Direct molecular targets incompletely validated	[51]
<i>Sorghum bicolor</i>	lncRNA–miRNA–target network	lncRNA sequencing; dual-luciferase assay; cis/trans target analysis	lncRNA-mediated upregulation of <i>SbYS1</i> (Cd chelate transporter)	Positive regulation of Cd accumulation and translocation	Field-scale functional validation lacking	[52]
<i>Triticum aestivum</i>	Cd-responsive lncRNAs	Strand-specific RNA sequencing; overexpression in <i>Arabidopsis thaliana</i>	69 cis-target pairs affecting photosystem II and antioxidant defense	Enhanced Cd tolerance via photosynthetic stabilization	Epigenetic chromatin context not resolved	[53]
<i>Thlaspi arvense</i>	Transcriptional memory (transgenerational plasticity)	RNA sequencing; weighted gene co-expression network analysis	401 transcriptional memory genes; sustained <i>CSD2</i> expression	Persistent elevated SOD activity across generations	DNA methylation or histone marks not directly mapped	[56]

* The proposed research limitations reflect this review’s critical synthesis and do not necessarily represent limitations explicitly stated in the cited studies.

Together, these studies suggest that Cd exposure can be associated with heritable alterations in DNA methylation patterns and sustained changes in gene expression that extend beyond the directly exposed generation. Although the number of well-controlled studies remains limited and mechanistic causality has not yet been fully established, available evidence is consistent with the possibility that Cd-induced epigenetic modifications may contribute to stress memory-like phenomena. Future investigations integrating methylome, chromatin, and functional genetic analyses across multiple generations will be essential to clarify the stability, reversibility, and ecological relevance of these transgenerational effects.

Section 2 provides the mechanistic basis of plant epigenetic regulation under cadmium stress, highlighting how chromatin-level modifications contribute to transcriptional reprogramming and stress memory. However, epigenetic plasticity in plants does not operate in isolation and is increasingly recognized as being responsive to external biotic cues. In Cd-contaminated environments, microbial communities represent a major but underexplored source of regulatory signals capable of modulating plant epigenetic states. Despite accumulating evidence that microbial interactions influence plant stress physiology, a coherent conceptual framework linking microbiome-derived signals to defined epigenetic modifications under Cd stress is still lacking. Building on this epigenetic foundation, Section 3 explores the plant–microbiome interface as a critical regulatory layer shaping epigenetic and transcriptional responses to cadmium toxicity.

3. Epigenetic Regulatory Frameworks at the Plant–Microbiome Interface Under Cadmium Stress

3.1. Microbiome-Mediated Modulation of Plant Stress Physiology Under Cadmium Exposure

3.1.1. Regulation of Cadmium Uptake, Transport, and Compartmentalization

A substantial body of evidence demonstrates that beneficial rhizosphere and endophytic microorganisms consistently alleviate Cd-induced growth inhibition across diverse plant species and experimental systems. Microbial inoculation commonly results in improved seed germination, enhanced biomass accumulation, preservation of photosynthetic capacity, and reinforcement of antioxidant defenses under Cd stress. These outcomes collectively indicate that plant-associated microbes substantially influence plant stress physiology, rather than merely buffering acute toxicity.

One major mechanism underlying microbiome-mediated Cd tolerance involves the regulation of Cd uptake, translocation, and compartmentalization. Several studies report reduced Cd accumulation in shoots and edible tissues following microbial application, achieved through restricted root-to-shoot transport or decreased Cd bioavailability in the rhizosphere. For instance, pre-sowing seed treatment of wheat with the Cd-tolerant endophyte *Bacillus subtilis* 10-4 enhanced lignin deposition in roots under Cd stress, thereby reinforcing cell wall barrier properties and restricting Cd translocation to aerial tissues [57]. Similarly, soil supplementation with carbonate-containing metabolites produced by the ureolytic bacterium *Ochrobactrum* sp. POC9 reduced Cd bioavailability via microbially induced carbonate precipitation processes, leading to substantial decreases in Cd uptake in both shoots and roots of *Petroselinum crispum* grown in Cd-contaminated soil [58].

However, microbial mitigation of Cd toxicity cannot be fully explained by metal immobilization or exclusion alone. In several plant–microbe systems, growth promotion and physiological recovery under Cd stress occur even in the presence of sustained or dynamically altered Cd accumulation patterns. In *Lycopersicon esculentum*, inoculation with *Pseudomonas aeruginosa* and *Burkholderia gladioli* significantly improved biomass, photosynthetic pigment content, and metal tolerance indices under Cd exposure, despite increased Cd uptake and enhanced thiol-based chelation responses [59]. Gene expression analyses further revealed that microbial inoculation attenuated Cd-induced upregulation of metal

transporter genes, indicating an active reprogramming of metal homeostasis rather than simple passive exclusion.

Such microbiome-driven modulation of cadmium uptake and translocation is increasingly viewed not only as a physiological adjustment but also as a potential upstream regulator of epigenetic plasticity. By reshaping intracellular metal burdens, redox balance, and stress signaling intensity, plant-associated microbes may indirectly influence chromatin organization and locus-specific DNA methylation dynamics. Altered cellular Cd thresholds may modulate the activation of stress-responsive transcription factors and chromatin remodelers, thereby affecting the recruitment or activity of DNA methyltransferases, demethylases, and histone-modifying enzymes. In this context, microbiome-mediated control of metal homeostasis may potentially contribute to priming-like processes that influence epigenetic responsiveness under chronic Cd exposure.

3.1.2. Transcriptional and Signaling Reprogramming Induced by Microbial Associations

Consistent with this regulatory perspective, *Pseudomonas fluorescens* treatment conferred pronounced Cd tolerance in *Arabidopsis thaliana* by enhancing growth, chlorophyll content, and reproductive output under Cd stress. This protection was associated with the induction of the metal resistance gene *AtPCR2*, whose overexpression conferred resistance not only to Cd but also to additional heavy metals [60]. These results suggest that transcriptional modulation contributes to microbiome-mediated Cd tolerance, beyond effects on metal bioavailability alone.

These transcriptional and signaling adjustments may create a regulatory framework within which microbiome-induced cues could interact with epigenetic mechanisms, potentially contributing to sustained gene expression dynamics under cadmium exposure.

3.1.3. Antioxidant, Redox, and Phytohormone-Mediated Modulation of Cd Stress Responses

Microbial associations modulate multiple physiological layers of Cd stress responses, including redox-related metabolism and phytohormone signaling. In *Lycopersicon esculentum*, inoculation with *Pseudomonas aeruginosa* and *Burkholderia gladioli* enhanced growth performance and photosynthetic pigment content under Cd exposure while increasing protein- and non-protein-bound thiol levels and modulating metal transporter gene expression [59]. These findings indicate that microbial inoculation can reshape metal chelation capacity and transporter regulation under Cd stress.

In cauliflower, application of Cd-tolerant bacterial consortia together with foliar jasmonic acid enhanced antioxidant enzyme activities, including superoxide dismutase, peroxidase, catalase, and polyphenol oxidase, while simultaneously improving shoot and root growth and reducing Cd accumulation in plant tissues [61]. Similarly, inoculation with the abscisic acid-producing bacterium *Azospirillum brasilense* elevated endogenous ABA levels, suppressed the expression of the metal transporter genes *IRT1* and *IRT2*, increased soil pH, and decreased bioavailable heavy metal pools, resulting in reduced Cd accumulation and substantial biomass gains across different soil types [62].

Given the sensitivity of DNA methylation, histone modification, and chromatin remodeling processes to redox and hormonal states, microbiome-mediated regulation of antioxidant and phytohormone pathways represents a plausible route through which microbial signals could shape epigenetic responses to cadmium stress.

Collectively, current studies demonstrate that plant-associated microbiomes substantially reprogram plant stress physiology under cadmium exposure through coordinated effects on metal transport, antioxidant capacity, and phytohormone signaling. Although these responses have primarily been characterized at physiological and transcriptional levels, their systemic integration and regulatory complexity suggest the possible involvement

of higher-order regulatory mechanisms. This provides a conceptual foundation for exploring epigenetic processes as potential mediators of microbiome-driven plant adaptation under cadmium stress, which is examined in the subsequent sections.

3.2. Microbiome-Derived Signals as Potential Modulators of Plant Epigenetic States Under Cd Stress

Cadmium stress induces extensive physiological and molecular reprogramming in plants, and growing evidence indicates that these responses are strongly influenced by rhizosphere and endophytic microorganisms. Beneficial microbes mitigate Cd toxicity through the production of phytohormones, organic acids, redox-active metabolites, and signaling molecules that regulate metal uptake, antioxidant capacity, and stress-responsive gene expression. While most available studies focus on transcriptional and metabolic outputs, the biochemical identity of these microbial signals, particularly those linked to acetyl-CoA metabolism, redox balance, and phytohormone signaling, suggests a plausible involvement of chromatin-level regulation as an additional layer of control.

From an epigenetic standpoint, the available evidence can be broadly categorized into direct and indirect microbiome-mediated regulatory modes. Direct evidence involves microbial signals that engage established chromatin-modifying pathways, such as histone acetylation or methylation, whereas indirect evidence reflects microbiome-driven modulation of phytohormone signaling, redox balance, and primary metabolism that secondarily shapes the epigenetic landscape under cadmium stress. Recent reviews highlight that heavy metal stress, including cadmium exposure, is frequently associated with changes in DNA methylation patterns, histone modifications, chromatin dynamics, and small-RNA-mediated regulation in plants, underscoring the emerging role of epigenetic mechanisms in plant adaptation to metal toxicity [14].

Beyond the classification of direct and indirect regulatory modes, quantitative analyses of microbial community topology provide additional insights into how microbial assemblages may influence host regulatory networks. Co-occurrence networks constructed from microbial communities in heavy-metal-polluted soils frequently exhibit distinct network properties, including altered node degree distribution, increased modularity, and shifts in keystone taxa, compared with networks in less contaminated environments. For example, heavy metal contamination has been shown to strengthen network complexity and modular structure, while simultaneously weakening positive interactions among keystone taxa and altering community composition [63]. These findings suggest that heavy metal stress reshapes microbial network topology in ways that reflect adaptive reorganization but may also influence community stability and functional capacity under contaminated conditions.

Such quantitative network characteristics may influence the consistency and intensity of microbial biochemical signaling to the plant host, thereby shaping hormonal, redox, and metabolic cues that are known to interact with chromatin regulators. Although direct mechanistic links between specific network metrics and host epigenetic outcomes remain limited, integrating microbial network topology with multi-omic host profiling is a promising frontier for understanding how community structure mediates systemic regulatory responses to cadmium stress.

Comparative insights from hyperaccumulator species such as *Pteris vittata* broaden the cross-species perspective of microbiome–metal–host interactions under cadmium stress. Although traditionally recognized as an arsenic hyperaccumulator, recent work demonstrates that *P. vittata* also exhibits distinct patterns of cadmium uptake and translocation dynamics under single and combined As–Cd exposure conditions, accompanied by shifts in rhizosphere microbial community composition and diversity [64]. These coordinated metal–microbiome interactions highlight hyperaccumulator systems as valuable comparative models for examining how metal exposure shapes host physiological and regulatory

adjustments. While direct evidence linking hyperaccumulator-associated microbiomes to defined chromatin modifications remains limited, such systems provide a promising framework for exploring whether specialized microbial assemblages correlate with sustained transcriptional and regulatory plasticity under cadmium stress.

Microbial modulation of jasmonic acid (JA) signaling represents a well-defined example of such regulation. Zhu et al. [65] demonstrated that the acetic acid-producing endophytic bacterium *Lysinibacillus fusiformis* Cr33 significantly reduced Cd accumulation in tomato plants, particularly by limiting root Cd uptake, through activation of JA signaling. Bacterial inoculation increased endogenous JA levels, downregulated Fe uptake-related genes and suppressed Fe acquisition systems, and reduced nitric oxide (NO) production in Cd-exposed roots. Comparable effects were observed following exogenous application of acetic acid or JA, whereas chemical inhibition of JA biosynthesis markedly attenuated the bacterium-mediated alleviation of Cd toxicity. Collectively, these findings support acetic acid-mediated JA signaling as a central microbial mechanism regulating Cd uptake under stress conditions.

Importantly, JA signaling is not only a regulator of metal uptake but is also associated with chromatin-level control of gene expression. Vincent et al. [66] showed that in *Arabidopsis thaliana*, components of the JA pathway functionally interact with HISTONE DEACETYLASE 6 (HDA6), influencing genome-wide patterns of histone modifications, including histone H4 acetylation (H4ac) and the repressive mark H3K27me3. MeJA treatment and HDA6 mutation were associated with coordinated changes in H4ac enrichment and H3K27me3 distribution at stress-responsive loci, highlighting overlapping roles of JA signaling and HDA6 in modulating transcriptional programs. These findings suggest that microbial activation of JA signaling under Cd stress, as reported by Zhu et al. [65], may engage established epigenetic regulatory frameworks rather than acting solely through transient hormonal effects. This provides a plausible mechanistic bridge between microbe-derived metabolic signals, hormone perception, and chromatin-based regulation of stress-adaptive gene expression.

Microbe-derived short-chain fatty acids represent an additional signaling axis linking microbial metabolism to host physiological regulation. Xiao et al. [67] showed that flooding-induced enrichment of *Clostridium* species in rice rhizospheres was associated with butyric acid-mediated activation of the phenylpropanoid pathway, resulting in enhanced lignification and suberization of root tissues and reduced root-to-shoot Cd translocation. Although chromatin-level changes were not examined in this study, butyrate has been reported in plant systems to influence histone acetylation status through inhibition of histone deacetylase activity. These observations raise the possibility that microbially derived short-chain fatty acids may contribute not only to metabolic reprogramming but also to epigenetic modulation of stress-adaptive pathways. Supporting the reported epigenetic activity of butyrate, exogenous sodium butyrate treatment increased histone acetylation marks (H3K9ac, H3K14ac, and H3K27ac) and transcriptionally activated phenylpropanoid biosynthetic genes in *Platycodon grandiflorus* [68]. Sodium butyrate also promoted the accumulation of phenylpropanoid-derived polyphenolic compounds. Collectively, these findings suggest a plausible mechanistic framework in which microbially produced butyrate may influence histone acetylation states, thereby facilitating transcriptional activation of phenylpropanoid-associated pathways. Such epigenetically mediated metabolic reprogramming could, in principle, contribute to reinforcement of root structural barriers and restriction of Cd mobility, although direct evidence under Cd stress conditions remains to be established.

Microbial influences on plant redox homeostasis may provide indirect routes to epigenetic regulation. Fan et al. [69] reported that under combined elevated CO₂ and Cd stress,

Brassica napus exhibited significant shifts in rhizosphere microbial composition alongside enhanced antioxidant enzyme activities, increased glutathione and ascorbate levels, and altered expression of stress-responsive transcription factors. Upregulation of glutathione-related genes and heavy metal ATPases further supported improved detoxification capacity under coupled stress conditions. Although causal links between microbial shifts and redox regulation were not directly established, these coordinated changes highlight redox metabolism as a potential interface between environmental signals, microbial dynamics, and stress-responsive gene regulation.

Cellular redox state and primary metabolism are recognized regulators of epigenetic enzyme activity, as metabolic flux and redox balance influence chromatin-modifying processes in plants [70]. Moreover, epigenetic factors such as DNA methyltransferases and histone-modifying enzymes are sensitive to redox-dependent modifications and require metabolic intermediates, including acetyl-CoA and S-adenosyl-methionine, for chromatin modification reactions [71]. Together, these insights suggest that microbiome-associated shifts in plant redox status and metabolism under Cd stress may modulate the biochemical environment that supports chromatin remodeling processes.

Although direct evidence for microbe-induced epigenetic modifications under cadmium stress remains limited, studies under non-metal stress conditions have clearly demonstrated that microbial signals can induce stable epigenetic changes in plants, providing important mechanistic precedents. For example, Chen et al. [72] demonstrated that plant growth-promoting bacteria induce region-specific DNA methylation changes in roots that persist even after microbial elimination and are required for sustained transcriptional reprogramming and growth promotion. Similar microbiome-induced reprogramming of DNA methylation and stress-responsive gene expression has been reported under drought stress [73], and additional work under drought and salinity conditions confirms that beneficial microbes can reshape antioxidant systems and transcriptional networks even without persistent colonization [74]. These observations provide a conceptual framework for hypothesizing that, under cadmium stress, microbial signals may similarly contribute to epigenetic priming of stress-responsive pathways, although this possibility remains to be explicitly tested. Representative studies demonstrating how distinct microbial groups and strategies modulate Cd dynamics in the rhizosphere and plant tissues are summarized in Table 2.

Table 2. Microbe-mediated strategies modulating Cd dynamics and plant performance.

Biological System	Microbial Strategy	Experimental/Analytical Approach	Mechanistic Insights	Physiological/Agronomic Outcomes	Proposed Research Limitations *	Reference
<i>Triticum aestivum</i> + <i>Bacillus subtilis</i> 10-4	Endophytic PGPR-mediated lignification and oxidative damage reduction	Seed pre-treatment; pigment, lignin, H ₂ O ₂ , lipid peroxidation and Cd quantification	Enhanced root lignification strengthens apoplastic barrier, restricting Cd translocation	Improved germination, biomass, pigment stability; reduced Cd accumulation	Field validation and molecular-level regulation of lignification under Cd stress remain unexplored	[57]
Soil– <i>Petroselinum crispum</i> + <i>Ochrobactrum</i> sp. POC9 (MCC)	Microbially induced carbonate precipitation (MICP)	Soil physicochemical analysis; Cd bioavailability assays; plant growth analysis	Cd stabilization via carbonate precipitation reduces bioavailable Cd fraction	Reduced Cd uptake (shoot/root); improved plant condition and soil microbial activity	Long-term stability of carbonate-bound Cd under variable field conditions requires assessment	[58]
<i>Solanum lycopersicum</i> + <i>Pseudomonas aeruginosa</i> , <i>Burkholderia gladioli</i>	PGPR-mediated transporter modulation and thiol-based detoxification	Growth analysis; thiol quantification; gene expression profiling of metal transporters	PGPR inoculation attenuated Cd-induced upregulation of metal transporter genes and enhanced thiol-mediated detoxification	Improved growth, pigment content, metal tolerance index	Specific transporter targets and long-term transcriptional regulation under field conditions remain unclear	[59]

Table 2. Cont.

Biological System	Microbial Strategy	Experimental/Analytical Approach	Mechanistic Insights	Physiological/Agronomic Outcomes	Proposed Research Limitations *	Reference
<i>Arabidopsis thaliana</i> + <i>Pseudomonas fluorescens</i>	Regulation of <i>AtPCR2</i> expression	In silico promoter analysis; qRT-PCR; transgenic overexpression lines	Bacteria treatment associated with increased <i>AtPCR2</i> transcript levels and enhanced Cd tolerance	Increased biomass, chlorophyll content, silique number	Upstream signaling linking bacterial cues to <i>AtPCR2</i> regulation remains unclear	[60]
<i>Brassica oleracea</i> (cauliflower) + <i>Klebsiella</i> spp. consortium (SS7+SS8) + jasmonic acid	Bacterial EPS, siderophore, and IAA production combined with foliar JA application	Jar trials; antioxidant enzyme assays; Cd quantification	Synergistic microbial–hormonal activation of antioxidant and detox pathways	Increased biomass; reduced shoot/root Cd concentration	Contribution of individual strains within consortium and long-term soil effects need clarification	[61]
<i>Brassica chinensis</i> (pak choi) + <i>Azospirillum brasilense</i>	Increased ABA levels associated with reduced <i>IRT1</i> and <i>IRT2</i> expression; increased soil pH	Multi-soil experiment; gene expression analysis; structural equation modeling	ABA elevation reduces Fe transporter-mediated Cd uptake; soil pH modulation decreases Cd availability	Strong biomass increase; reduced multi-metal accumulation	Durability of ABA-mediated regulation across cropping cycles remains unknown	[62]
<i>Solanum lycopersicum</i> + <i>Lysinibacillus fusiformis</i> Cr33	Acetic acid-mediated JA signaling; suppression of NO and Fe uptake systems	Hormone quantification; gene expression; chemical inhibition assays	JA-dependent suppression of Fe transport limits Cd uptake	Reduced root Cd accumulation; enhanced tolerance	Broader applicability across species and environmental contexts requires validation	[65]
<i>Oryza sativa</i> under flooding + <i>Clostridium</i> sp.	Butyric acid-induced phenylpropanoid pathway; apoplastic barrier formation	WGCNA; transcriptome–metabolome integration; Cd translocation assays	Microbial butyrate enhances suberization and lignified xylem formation	Reduced root-to-shoot Cd translocation	Stability of <i>Clostridium</i> -driven barrier formation under fluctuating water regimes needs study	[67]
<i>Brassica napus</i> under ECO ₂ conditions	CO ₂ -driven modulation of antioxidant system and rhizosphere microbial composition	Transcriptomics; metabolomics; antioxidant assays; Cd quantification	ECO ₂ increases Cd uptake but enhances detoxification via glutathione and ATPase pathways	Increased biomass and antioxidant capacity	Mechanistic separation of ECO ₂ and microbiome contributions remains limited	[69]
<i>Oryza sativa</i> + <i>Stenotrophomonas</i> R5	Enhanced microbial network complexity and cooperation	Molecular ecological network analysis	Increased microbial connectivity correlates with reduced Cd absorption	Reduced plant Cd content under Cd stress	Causal relationship between network topology and Cd reduction remains to be experimentally confirmed	[75]
<i>Sedum alfredii</i> ecotypes	Phenolic compound-mediated shaping of keystone operational taxonomic units (OTUs)	Comparative microbiome analysis; network analysis	Ecotype-specific microbial network complexity associated with improved growth under Cd stress	Higher biomass in Cd-accumulating ecotype	Direct functional validation of keystone OTUs is required	[76]
<i>Oryza sativa</i> under Cd gradient	Concentration-dependent rhizosphere community shifts	Cd speciation analysis; microbial diversity profiling	Rhizosphere-mediated effects shift from stress alleviation at moderate Cd to stress intensification at high Cd	Biomass recovery at moderate Cd; inhibition at high Cd	Mechanisms underlying threshold-dependent microbial functional shifts remain unresolved	[77]
Field cultivars of <i>Oryza sativa</i>	Metabolite–microbiome interactions; cultivar-dependent differences in nutrient cycling	Field experiment; metabolomics; metagenomics	More diverse and interconnected microbial networks associated with Cd immobilization and antioxidant defense in low-accumulating cultivars	Reduced Cd accumulation in low-accumulating cultivars	Functional causality between specific metabolites and microbial taxa requires validation	[78]

* The proposed research limitations reflect this review's critical synthesis and do not necessarily represent limitations explicitly stated in the cited studies.

Collectively, these findings suggest that microbiome-derived signals under cadmium stress are unlikely to function as direct epigenetic writers, but instead modulate the biochemical and signaling milieu in which chromatin regulation operates. By modulating phytohormone pathways, organic acid pools, and cellular redox balance, beneficial microbes may modulate histone acetylation, methylation, and chromatin accessibility during

Cd stress. This emerging framework highlights a critical knowledge gap and underscores the need for integrative studies that directly link microbial signals to defined chromatin modifications and epigenetic priming under Cd stress.

3.3. Microbial Network Dynamics and the Potential for Epigenetic Plasticity in Cd-Stressed Plants

Beyond the presence or absence of individual microbial taxa, the organization and interaction structure of rhizosphere and endophytic microbial communities have emerged as a key correlate of plant performance under Cd stress. Network-based ecological analyses increasingly demonstrate that microbial connectivity, interaction strength, and cooperative structure are associated with reduced Cd accumulation and improved plant growth. These findings indicate that community-level microbial organization, rather than taxonomic composition alone, plays an important role in shaping plant responses to Cd exposure.

Evidence for this relationship is provided by network analyses in rice systems. Zheng et al. [75] showed that inoculation with the Cd-resistant endophytic bacterium *Stenotrophomonas* R5 markedly altered microbial network topology in both roots and shoots, leading to increased network complexity and connectivity. Importantly, higher network complexity was negatively correlated with plant Cd accumulation, suggesting that more interconnected microbial communities may contribute to reduced Cd uptake and translocation, potentially through synergistic plant–microbiome interactions.

Comparable patterns have been observed across plant species and ecotypes differing in Cd-handling strategies, although the functional implications of microbial network complexity appear context-dependent. Shao et al. [76] demonstrated that under Cd stress, the Cd-accumulating ecotype of *Sedum alfredii* harbored rhizosphere microbial networks with significantly higher network complexity and a greater number of positive associations compared to the non-accumulating ecotype. Network complexity was positively correlated with plant performance, and the accumulating ecotype exhibited greater biomass under Cd stress. In this hyperaccumulator system, increased microbial network complexity may reflect coordinated plant–microbiome adaptation supporting high Cd tolerance and accumulation capacity.

The relationship between rhizosphere microbial community structure and plant Cd responses is further modulated by stress intensity. Cheng et al. [77] demonstrated that rhizosphere microbial communities respond to increasing soil Cd concentrations in a non-linear, concentration-dependent manner. At moderate Cd levels, rhizosphere activity was associated with reduced dissolved Cd availability and partial recovery of rice biomass, whereas high Cd concentrations led to diminished microbial diversity, altered community structure, and exacerbated Cd toxicity. These results indicate that the functional role of microbial communities can shift from protective to detrimental depending on Cd exposure levels, emphasizing the dynamic nature of plant–microbiome interactions under metal stress.

Host genotype also plays a significant role in shaping microbial network properties. In contrast to the hyperaccumulator model described above, Wang et al. [78] demonstrated that low-Cd-accumulating (LA) rice cultivars harbored rhizosphere microbial communities that were more diverse and highly interconnected than those associated with high-Cd-accumulating (HA) cultivars. In this agronomic context, enhanced microbial diversity and network connectivity in LA cultivars were associated with improved nutrient cycling, altered metabolite profiles, and reduced Cd uptake. These findings suggest that microbial network complexity may support either enhanced Cd tolerance and accumulation (as in hyperaccumulators) or reduced Cd uptake (as in crop cultivars), depending on species-specific physiological strategies and rhizosphere microecosystem context.

Although these studies consistently demonstrate associations between microbial network complexity and plant performance under Cd stress, they do not yet resolve the

molecular mechanisms by which plants integrate microbially derived environmental signals. The structured organization of these communities implies exposure to coordinated biochemical environments shaped by microbial metabolism, metabolite exchange, and nutrient cycling. In plants, chromatin-based regulatory systems—including DNA methylation and histone modifications—are increasingly recognized as mechanisms enabling transcriptional plasticity and defense- and stress-related memory-like responses under recurrent environmental stimuli [28,79]. In parallel, reviews of plant growth-promoting microorganisms under abiotic stress conditions suggest that microbial interactions may intersect with phytohormone signaling and epigenetic modulation pathways, potentially contributing to stress-adaptive transcriptional responses [80]. Supporting the broader plausibility of epigenetically mediated metabolic plasticity, studies in endophytic fungi demonstrate that chromatin remodeling can activate secondary metabolic pathways and alter signaling capacities [81]. Within this framework, network-level microbial stability under Cd stress could plausibly facilitate epigenetic reinforcement of gene expression programs related to metal exclusion, detoxification, or transport regulation, even in the absence of direct chromatin-level evidence. While direct chromatin-level evidence under Cd–microbe co-regulation remains limited, the integration of microbial ecology and plant epigenetics provides a mechanistically coherent hypothesis that is schematically illustrated in Figure 1.

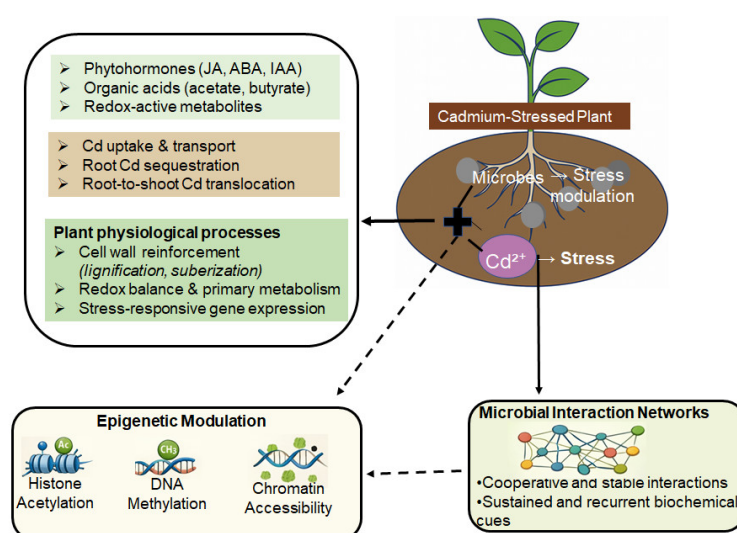


Figure 1. Conceptual framework illustrating putative microbe-driven epigenetic regulation of plant responses under cadmium stress. Cadmium (Cd^{2+}) exposure induces stress in plants by affecting metal uptake, sequestration, and root-to-shoot translocation. In parallel, rhizosphere and endophytic microbes interact with Cd-stressed roots and mitigate toxicity through the production of phytohormones (e.g., jasmonic acid, abscisic acid, auxin), organic acids (acetate, butyrate), and redox-active metabolites. These microbial signals modulate key plant physiological processes, including cell wall reinforcement (lignification and suberization), redox balance, primary metabolism, and stress-responsive gene expression, ultimately contributing to reduced Cd accumulation and improved stress tolerance. Microbial communities are depicted as structured interaction networks characterized by cooperative interactions and sustained biochemical signaling, providing a persistent rhizosphere environment rather than transient cues. Based on established links between hormonal, metabolic, and redox signaling and chromatin regulation, these persistent microbe-mediated cues are proposed to converge on epigenetic modulation, including changes in histone acetylation, DNA methylation, and chromatin accessibility. Solid arrows denote relationships supported by experimental evidence, including microbial modulation of Cd transport, antioxidant capacity, and hormone-mediated signaling pathways. Dashed arrows indicate proposed but not yet experimentally validated links between microbial interaction networks and chromatin-level regulation under Cd stress.

3.4. Microbiome-Mediated Epigenetic Regulation Under Cd Stress

As outlined in Section 3.2, microbiome-derived signals, including phytohormones, organic acids, and redox-modulating metabolites, provide multiple biochemical entry points through which plant epigenetic states could plausibly be influenced under Cd stress. Section 3.3 further demonstrated that these signals are not transient or isolated, but are embedded within structured and persistent microbial interaction networks that correlate strongly with plant performance, Cd accumulation, and stress resilience. Together, these observations raise a central mechanistic question: can microbiome-derived cues directly reprogram plant epigenetic or epitranscriptomic landscapes under Cd exposure, thereby contributing to sustained stress adaptation rather than short-term physiological buffering?

To date, direct experimental evidence addressing this question remains limited, but critically informative. Xu et al. [82] provided one of the clearest mechanistic demonstrations of microbiome-driven epigenetic reprogramming under Cd stress. Using rice and *Solanum nigrum*, the authors identified a cross-kingdom signaling cascade described as a “root ROS–microbial IAA–root DNA methylation” axis. Cd exposure triggered reactive oxygen species (ROS) accumulation in plant roots, which in turn stimulated indole-3-acetic acid (IAA) biosynthesis in associated plant growth-promoting bacteria. Microbe-derived IAA subsequently attenuated excessive root ROS levels and induced the expression of key components of the plant DNA methylation machinery, including *MET1a/MET1b*, *DRM2*, *CMT2/CMT3*, *DDM1a/DDM1b*, and *ROS1*. Whole-genome bisulfite sequencing revealed increased global methylation levels in CG, CHG, and CHH contexts in inoculated roots, with differentially methylated regions enriched in hormone response and gene regulatory processes. Induced expression of DNA methylation-related genes involved both ROS-dependent (*ROS1*, *DRM2*, *CMT3*, *DDM1a/b*) and ROS-independent (*MET1a/b*, *CMT2*) components. These findings support a mechanistic connection between microbial metabolism and host epigenetic machinery under Cd stress (Figure 2A). While this study provides compelling mechanistic evidence in rice and *S. nigrum*, its broader applicability across plant species, microbial consortia, and soil systems remains to be determined.

At the RNA level, Han et al. [83] provided complementary evidence that plant-associated microbes can reshape epitranscriptomic regulation during Cd exposure. In soybean, rhizobial symbiosis largely alleviated Cd-induced root growth inhibition without significantly altering root Cd concentrations, indicating that microbial protection was not primarily driven by metal exclusion. Transcriptome-wide profiling of N⁶-methyladenosine (m⁶A) RNA methylation revealed that Cd stress broadly increased m⁶A deposition, whereas rhizobial association reprogrammed m⁶A patterns on transcripts involved in hormone signaling, ROS homeostasis, MAPK cascades, and abiotic stress responses. Integration of m⁶A methylome and transcriptome datasets identified gene subsets whose RNA methylation status and expression levels were coordinately altered under Cd stress in the presence of rhizobia, supporting the conclusion that microbial symbiosis is associated with modulation of post-transcriptional regulatory layers during heavy metal stress (Figure 2B).

Beyond the two studies discussed above, direct experimental evidence linking plant-associated microbes to stable epigenetic or epitranscriptomic reprogramming under Cd stress remains scarce. Notably, this limitation reflects not a lack of microbiome influence on plant stress responses, but rather the current methodological gap between well-documented microbiome-driven modulation of phytohormone signaling, redox balance, and microbial network structure (Sections 3.2 and 3.3) and chromatin- or RNA-level regulatory readouts. Thus, microbiome-mediated epigenetic regulation under Cd stress is biochemically plausible and increasingly supported by targeted studies, yet remains insufficiently resolved at the molecular level.

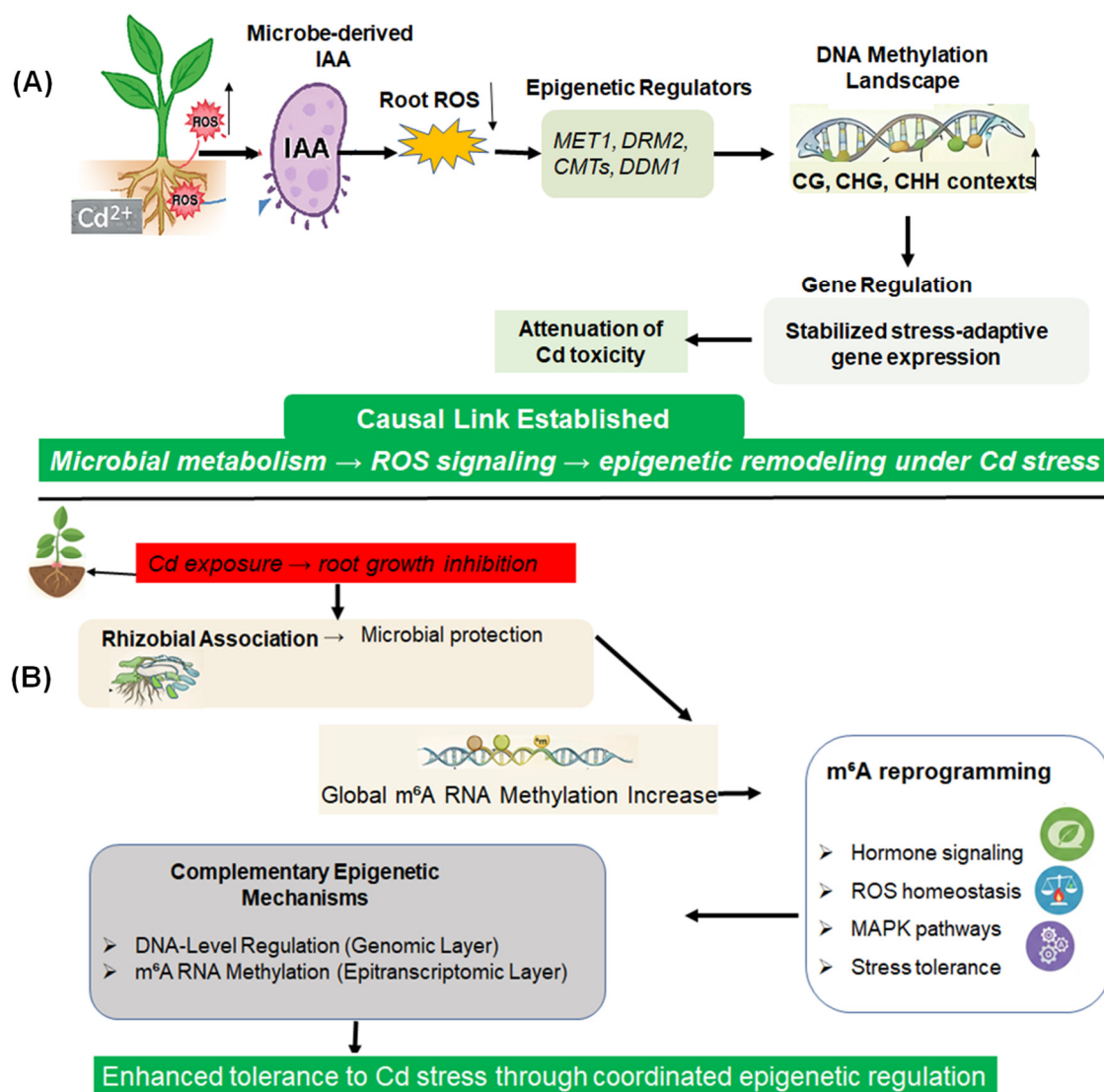


Figure 2. (A) Microbiome-mediated epigenetic remodeling under cadmium (Cd) stress involves a root ROS–microbial IAA–DNA methylation axis. Cd²⁺ exposure induces reactive oxygen species (ROS) accumulation in plant roots, which stimulates indole-3-acetic acid (IAA) biosynthesis in associated plant growth-promoting bacteria. Microbe-derived IAA modulates root ROS homeostasis and promotes the expression of key DNA methylation regulators, including *MET1*, *DRM2*, *CMTs*, and *DDM1*. This results in enhanced DNA methylation across CG, CHG, and CHH sequence contexts, contributing to the coordinated regulation of stress-responsive genes and functional attenuation of Cd toxicity. Genetic and epigenomic evidence supports mechanistic evidence linking microbial metabolism, ROS signaling, and plant epigenetic remodeling under Cd stress. (B) In parallel, rhizobial symbiosis reshapes cadmium-induced N⁶-methyladenosine (m⁶A) RNA methylation patterns in soybean, leading to transcriptome-wide reprogramming of genes involved in hormone signaling, ROS homeostasis, MAPK cascades, and stress responses. Together, DNA-level and RNA-level epigenetic regulation highlight a coordinated multilayered mechanism underlying microbe-mediated adaptation to Cd stress.

On this basis, the available evidence supports a conceptual model in which microbiome-derived signals do not act as direct epigenetic “writers,” but rather function upstream by shaping the metabolic, hormonal, and redox environments that determine chromatin accessibility and epigenetic enzyme activity. Persistent exposure to microbial metabolites, hormones, and redox cues generated by stable microbial interaction networks may therefore facilitate epigenetic stabilization of stress-responsive transcriptional

programs, potentially contributing to stress priming, memory formation, and long-term adaptive plasticity under chronic Cd exposure.

Consequently, microbiome-driven epigenetic and epitranscriptomic regulation under Cd stress represents an emerging research frontier. Addressing this gap will require integrative experimental frameworks that simultaneously resolve microbial community structure, interkingdom signaling molecules, and host chromatin- or RNA-level regulatory dynamics. Such approaches will be essential not only to establish causality, but also to determine whether microbiome-induced epigenetic modifications contribute to stress memory, transgenerational inheritance, or durable adaptation in Cd-contaminated environments.

4. Future Perspectives

4.1. Fundamental Research Directions

Although significant progress has been made in understanding plant responses to Cd stress, the integration of plant–microbiome interactions with epigenetic regulation is still at an early stage. Existing studies clearly show that beneficial microorganisms strongly influence plant physiology under Cd exposure, and recent evidence suggests that plant-associated microbes may influence plant DNA and RNA methylation patterns under Cd stress. However, such mechanistic evidence is currently limited to a small number of experimental systems. The mechanistic links connecting microbial signals, epigenetic regulation, and long-lasting stress tolerance therefore remain poorly resolved at the level of causal and temporally stable regulatory mechanisms.

A major priority for future research is to clarify whether microbiome-induced epigenetic changes act as primary regulators of Cd tolerance or mainly function to stabilize and reinforce stress-induced transcriptional responses over time. Disentangling cause–effect relationships will require time-resolved analyses and tissue- or cell-specific epigenomic approaches, particularly in roots where Cd perception and microbial interactions are most active.

Another important research gap concerns the role of microbial community structure. Increasing evidence links complex and stable microbial networks to improved plant performance under Cd stress. However, it remains unclear whether persistent microbial community configurations actively shape plant epigenetic states through sustained and coordinated biochemical signaling. Integrating microbial network parameters (e.g., connectivity, modularity, and network stability) with host chromatin profiling may help determine whether long-term exposure to structured microbiomes contributes to stable epigenetic reprogramming in plants.

The potential involvement of plant-associated microbes in epigenetic stress memory and transgenerational inheritance also warrants further investigation. While Cd-induced DNA methylation changes and heritable tolerance traits have been reported, the contribution of the microbiome to the establishment or maintenance of these epigenetic marks across generations remains largely unexplored. Carefully designed multigenerational experiments that manipulate microbial communities will be essential to verify causal relationships and to determine whether microbiome-associated epigenetic modifications persist beyond the directly exposed generation.

4.2. Applied and Translational Research Directions

From an applied perspective, future strategies for managing Cd-contaminated soils may benefit from shifting the focus from metal exclusion alone toward enhancing regulatory resilience. Screening and selecting microbial strains or consortia with the potential to modulate host epigenetic and epitranscriptomic states could represent a complementary strategy for improving plant performance under chronic metal stress. Such approaches may support soil remediation and sustainable crop production in contaminated environments.

However, translating these concepts into agricultural practice will require rigorous validation under field conditions, long-term stability assessments of microbial–plant associations, and consideration of soil physicochemical variability and microbiome dynamics across environments.

5. Conclusions

Cadmium contamination remains a persistent challenge for agricultural sustainability, food safety, and ecosystem health. Extensive research has established that plants deploy complex physiological, molecular, and biochemical defense strategies to cope with Cd toxicity. In parallel, growing evidence indicates that epigenetic regulation plays an important role in shaping Cd-responsive gene expression, stress acclimation, and, in some cases, transgenerational stress memory. DNA methylation dynamics, histone modifications, chromatin remodeling, and small-RNA-mediated regulation collectively contribute to the plasticity of plant responses under Cd stress. At the same time, the plant-associated microbiome has emerged as a powerful modulator of Cd bioavailability, uptake, and toxicity. Beneficial microbes alleviate Cd stress through diverse mechanisms, including metal immobilization, modulation of phytohormone signaling, enhancement of antioxidant capacity, and metabolic reprogramming. However, most microbiome-focused studies have primarily emphasized physiological and agronomic outcomes, with limited consideration of chromatin-level regulation in the host plant. By synthesizing evidence from epigenetics and plant–microbiome research, this review highlights a critical conceptual gap: the lack of direct mechanistic links connecting microbial signals to epigenetic reprogramming under Cd stress. Although recent studies suggest that microbe-derived phytohormones, organic acids, redox-active metabolites, and signaling molecules can influence plant transcriptional networks, direct experimental evidence demonstrating stable, microbe-induced epigenetic modifications under Cd exposure remains limited. Nevertheless, accumulating indirect evidence supports a model in which microbiome-mediated modulation of hormonal balance, redox status, and metabolic fluxes creates a biochemical environment conducive to epigenetic regulation. Rather than acting as direct epigenetic writers, microbial cues are more likely to function upstream, by modulating cellular metabolism and signaling pathways that influence chromatin accessibility and transcriptional plasticity. By integrating these lines of evidence, this review proposes an integrated regulatory framework for microbiome–plant epigenetic interactions under cadmium stress, thereby linking microbial community dynamics, host chromatin regulation, and stress-adaptive outcomes into a coherent mechanistic continuum. This framework forms a conceptual closed loop in which Cd exposure reshapes the microbiome, microbiome-derived signals modulate plant metabolic and hormonal states, and these shifts condition epigenetic regulation that ultimately feeds back into stress tolerance and adaptive capacity. Such interactions may contribute to stress memory, adaptive potential, and long-term plant resilience in Cd-contaminated environments.

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