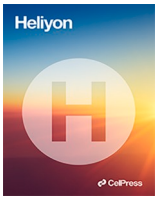
Heliyon 10 (2024) e29140

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

From genes to ecosystems: Decoding plant tolerance mechanisms to arsenic stress

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ARTICLE INFO

Keywords:
Arsenic stress
Abiotic stress
Plant stress response
Genomic and molecular mechanisms
Defense mechanisms
Arsenic toxicity

ABSTRACT

Arsenic (As), a metalloid of considerable toxicity, has become increasingly bioavailable through anthropogenic activities, raising As contamination levels in groundwater and agricultural soils worldwide. This bioavailability has profound implications for plant biology and farming systems. As can detrimentally affect crop yield and pose risks of bioaccumulation and subsequent entry into the food chain. Upon exposure to As, plants initiate a multifaceted molecular response involving crucial signaling pathways, such as those mediated by calcium, mitogen-activated protein kinases, and various phytohormones (e.g., auxin, methyl jasmonate, cytokinin). These pathways, in turn, activate enzymes within the antioxidant system, which combat the reactive oxygen/nitrogen species (ROS and RNS) generated by As-induced stress. Plants exhibit a sophisticated genomic response to As, involving the upregulation of genes associated with uptake, chelation, and sequestration. Specific gene families, such as those coding for aquaglyceroporins and ABC transporters, are key in mediating As uptake and translocation within plant tissues. Moreover, we explore the gene regulatory networks that orchestrate the synthesis of phytochelatins and metallothioneins, which are crucial for As chelation and detoxification. Transcription factors, particularly those belonging to the MYB, NAC, and WRKY families, emerge as central regulators in activating As-responsive genes. On a post-translational level, we examine how ubiquitination pathways modulate the stability and function of proteins involved in As metabolism. By integrating omics findings, this review provides a comprehensive overview of the complex genomic landscape that defines plant responses to As. Knowledge gained from these genomic and epigenetic insights is pivotal for developing biotechnological strategies to enhance crop As tolerance.

1. Introduction

Arsenic (As), an element found ubiquitously in the environment, has its distribution and toxicity amplified by both natural geological processes, such as mineral dissolution from groundwater leaching, tectonic activities, and volcanic emissions, and human

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https://doi.org/10.1016/j.heliyon.2024.e29140
Received 15 November 2023; Received in revised form 28 March 2024; Accepted 1 April 2024
Available online 2 April 2024

actions, notably mining, use of As-based pesticides, and industrial activities [1]. These anthropogenic sources have significantly augmented the As concentrations in soils and waters, making As pollution an acute environmental concern [2]. The Environmental Protection Agency (EPA) sets a maximum concentration of 10 parts per million (ppm) for As in drinking water. However, reports have revealed elevated As levels worldwide, highlighting a global challenge [3–6]. Such pervasive contamination has led the U.S. Toxic Substances and Diseases Registry (2022) to rank As as a top environmental contaminant due to its association with severe health conditions, including cancer and cardiovascular diseases [7], with dietary intake of As-tainted foodstuffs being a principal human exposure pathway [8].

Plants, which absorb As primarily from contaminated groundwater, serve as an entry point for As into the food chain, with documented impacts on crop development, yield, and safety [9]. Its speciation and environmental conditions dictate the mobility and uptake of As in plants, such as soil pH and redox status, influencing the prevalence of its inorganic forms, arsenate (AsV) and arsenite (AsIII) [10]. The dynamic between AsV, a phosphate analog, and AsIII, which utilizes aquaglyceroporin transporters to enter roots, forms the basis for understanding As interactions within plants [11,12]. Once inside, As navigates through the plant via transport proteins, and its detoxification involves complexation with thiol-rich peptides, leading to vacuolar sequestration [13–15].

The plant response to As is not merely passive; it activates a network of defensive mechanisms, including the detoxification and sequestration strategies seen in As hyperaccumulators like *Pteris vittata* and the signaling pathways involving calcium and MAPKs, integral for initiating a cascade of protective responses [16–18]. Plant adaptation and survival in As-polluted environments rely on these responses to modulate oxidative stress and enhance the resilience of plant systems [19].

The interaction between plants and As begins with its bioavailability and hinges on its oxidation state and chemical form. As can exist inorganic or organic forms, each with distinct environmental behaviors and toxicities. As(V), prevalent in oxidizing conditions, becomes immobilized by soil minerals, whereas As(III) predominates in reducing conditions and exhibits higher solubility and biological availability, making it the more harmful form [20–22]. This review aims to synthesize the growing knowledge of plant interactions' genomic and epigenetic aspects with As, focusing on the molecular underpinnings of As tolerance and its implications for phytoremediation. We aim to elucidate the complex interplay between As and plant systems through an integrative genomic lens. We provide insights for developing strategies to alleviate As contamination and its impacts on agriculture and human health.

2. Genomic insights into arsenic uptake transporters in plants

As uptake in plants primarily hinges on specific cell membrane transporters that facilitate the movement of As into the plant's cytoplasm [11]. Transporters involved in As uptake are encoded by genes resembling those responsible for essential nutrient absorption, leading to inadvertent As uptake (Table 1). Genomic studies have highlighted PHT genes (phosphate transporters), such as *AtPHT1;1* and *AtPHT1;4* in *Arabidopsis thaliana*, that facilitate the uptake of AsV, mimicking the entry of phosphate [23]. This phenomenon is not unique to *Arabidopsis*—other species, such as *P. vittata* and *Panax notoginseng,* also demonstrate an increase in PHT genes under As(V) exposure [24,25]. In *Triticum aestivum*, it has been reported that reducing the expression of *TaPHT1;9* gene correlates with a dip in As accumulation, suggesting a genetic method for enhancing tolerance [26].

Moreover, aquaglyceroporin gene families, specifically nodulin 26-like intrinsic (NIPs) transporters, play a crucial role in As(III) uptake in plant roots. These transporters, known for their primary function in water and glycerol transport, also facilitate the entry of As(III) into the roots [27]. It has been reported that the knockout mutants *AtNIP3;3* and *AtNIP7;1* exhibit higher As(III) tolerance and

Table 1
Classification of gene transporters involved in arsenic uptake in plants.

Gene ID	Gene Name	Category	Related As specie uptake	Source	Plant Tissue	Localization	Reference
Os02g0745100	*Lsi1*	Membrane silicon transporter	Arsenite and methylated As	*Oryza sativa*	Distal end of exodermal and endodermal cells	Cell membrane	[11]
At5g43350 MN260326.1	*PHT1;1*	Membrane Phosphate transporter	Arsenate	*Pteris vittata* *Salix eriocephala* *A. thaliana*	Root cells, hydathodes, axillary buds, and peripheral endosperm of germinating seeds	Cell membrane	[24,36,37]
At5g43360 KM192137.1	*PHT1;3*						
At2g38940 LOC_4331634	*PHT1;4* *PHT1;12*						
At4g19030 *At2g17750.1*	*NIP1;1*	Aquaporin	Arsenite	*A. thaliana* *Oryza sativa*	Root cells	Cell membrane	[28,35,38]
At4g18910 LOC_4327074	*NIP1;2*						
Os08g0152000	*NIP3;3*						
Os09g0505400 Os05g0576900	*PIN5c* *PIN10B*	Auxin transporter	Arsenite	*Oryza sativa*	Root cells	Cell membrane	[39]
At1g01620 Os02g0823100	*PIP1;3*	Plasma membrane intrinsic proteins	Arsenite	*Oryza sativa* *A. thaliana*	Root cells	Cell membrane	[33,34]
At3g53420	*PIP2;2*						
At5g60660	*PIP2;4*						
LOC_Os04g16450	*PIP2;6*						
At4g35100	*PIP2;7*						

lower As content in *Arabidopsis* than the control [28,29]. This genomic response is similar in *Oryza sativa*, where *OsNIP3;2* mutants show less As(III) root accumulation [30]. Moreover, *NIP1;1* was initially identified in the plasma membrane; however, it has also been found in the endoplasmic reticulum (ER) of *Arabidopsis,* playing a crucial role in As(III) trafficking within the plasma membrane through interaction with the SNARE protein SYP51 (Soluble N-ethylmaleimide-sensitive factor attachment protein receptor) [31]. This interaction modifies the ER and vacuole's ability to accumulate As(III), essential for As tolerance in both root and shoot tissues [32]. Besides, the involvement of plasma membrane intrinsic proteins (PIP), the most abundant aquaporin, in As(III) uptake has been observed. According to Modareszadeh et al. [33], overexpression of the *AtPIP2;2* gene in *Arabidopsis* enhances As(III) transport, while in rice, PIP genes such as *OsPIP2;4*, *OsPIP2;6*, and *OsPIP2;7* have shown increased tolerance to As(III). Additionally, during short-term As(III) exposure, *Arabidopsis* expressing *OsPIP2;6* showed increased As(III) uptake and export activities in roots, indicating that these *OsPIPs* may act as bidirectional

Transporters for As(III) [34]. Likewise, it has been reported the synergistic action of *NIP1;1* and *PIP1;1* transporters in *Nicotiana tabacum* plants boost As tolerance [35].

Furthermore, due to the chemical kinship between arsenite and silicic acid, silicon (Si) transport-related genes also play their part in As(III) uptake. As(III) is inadvertently taken up and transported in rice roots via the silicic acid transporters *OsLsi1* and *OsLsi2* [11]. It has been suggested that *PvTIP4;1*, a tonoplast intrinsic protein (TIP) aquaporin from *P. vittata*, may also be involved in As(III) uptake due to its function and location within the cell [40]. Moreover, a recent study has also reported that the PIN-FORMED (PIN) protein family of auxin transporters (*OsPin5c* and *OsPIN10b)* may participate in As uptake [39].

Regulatory pathways inside the cell, such as those involving GABA (gamma-aminobutyric acid), are instrumental in modulating As uptake. GABA, a known regulator of anion channels and a stress-response signaling molecule, has been shown to suppress the expression of As-related transporter genes *Lsi1* and *Lsi2*, thus modulating the gene activity as a countermeasure to As(III) uptake [41]. *OsGrx_C7*, which encodes glutaredoxin, also shapes the transcription landscape of aquaporin transporter genes in the presence of As, thereby controlling the As transport from roots to shoots [42]. In *O. sativa*, the MYB transcription factor *OsARM1* regulates As-associated transporter genes such as *OsLsi1*, *OsLsi2*, and *OsLsi6* [43]. This study also revealed the presence of MYB-binding sites in the promoters of these genes, highlighting their crucial role in regulating As uptake and transport.

Similarly, the transcription factor *Myb40* is recognized for its influence in downregulating *PHT1;1* expression, reducing As(V) uptake and boosting thiol peptide concentrations, which further promotes the expression of the *ABCC1* transporter gene responsible for As vacuolar transport and storage [44]. Additionally, it has been reported that *WRKY6* TF is an arsenate-responsive TF that arbitrates *PHT1* transporter gene regulation and prevents transposon activation induced by As(V) [45]. However, *Arabidopsis WRKY45*

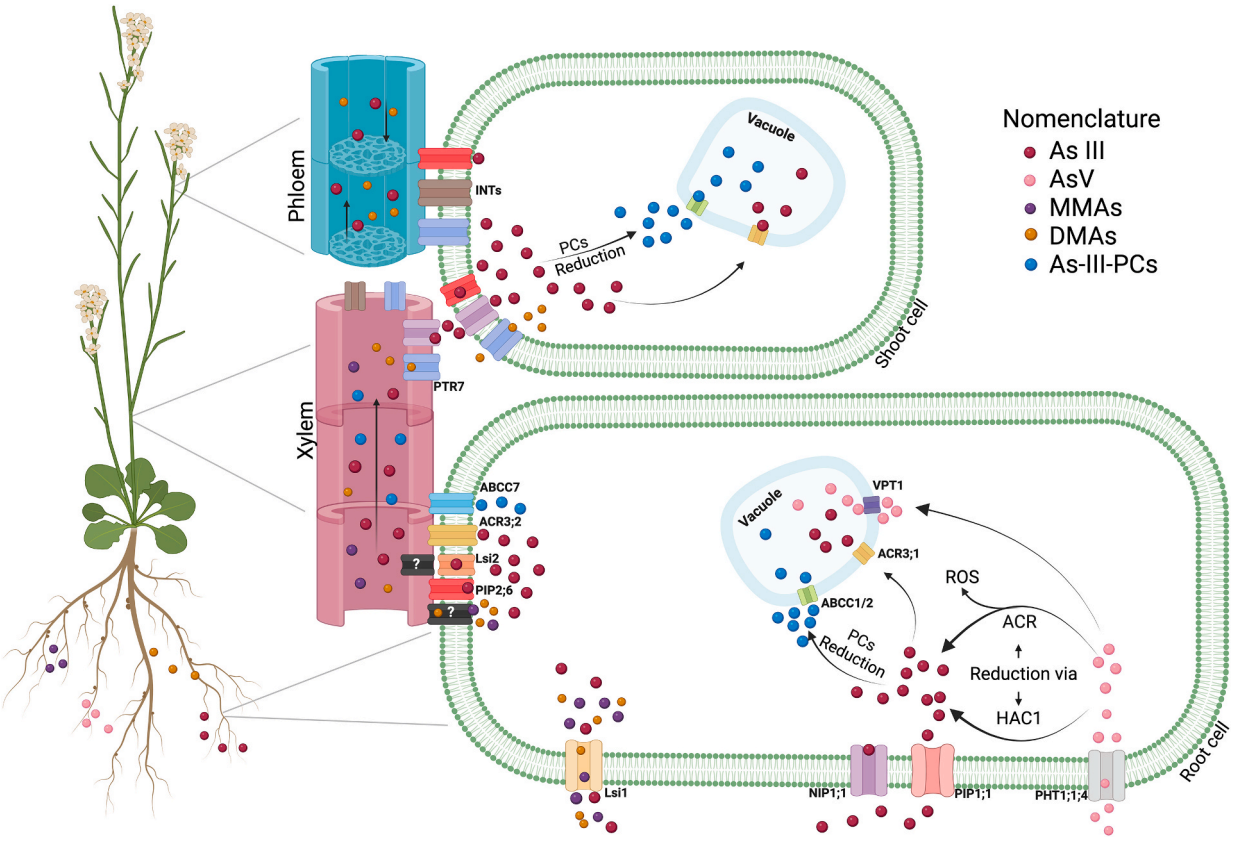

Fig. 1. Transporters involved in the short and long translocation of different As species in root and shoot tissues.

TF activates *PHT1;1* expression in response to phosphate starvation [46], suggesting that *WRKY* TF may play an important role in regulating As(V) uptake [47].

3. Arsenic translocation and storage

After undergoing the preceding mechanisms, when primary root cells still contain a high concentration of As, plants can facilitate the movement of As from the roots to shoot tissues through the xylem and phloem, employing various types of transporters, this process is referred to as long-distance translocation [48]. Moreover, plants can also biotransform arsenic into different species and then store them in vacuoles with the assistance of vacuole-membrane transporters; this mechanism is known as short-distance translocation [49]. Although long and short translocation mechanisms are recognized, crucial steps on both transport mechanisms remain unclear.

3.1. Short-distance translocation of arsenic

Cellular membrane transporters play a pivotal role in the short-distance transport of As, where the influx and efflux depend on the As speciation. For instance, the As (III) efflux permease encoded by the *ACR3* gene in *P. vittata* has been identified as a mediator of As (III) transport to the vacuole [50]. Knocking out the *ACR3* gene results in an As (III)-sensitive phenotype, highlighting the critical role of *ACR3* in the tolerance mechanisms of As (III) transport to vacuole storage [51]. Similarly, the expression of *ACR3* in tonoplast membranes enhances the accumulation of As in vacuoles of *Nicotiana tabacum* root cells, serving as a resistance mechanism, as depicted in Fig. 1 and Table 2 [52].

Another type of As transporter belongs to the ATP-binding cassette (ABC) transporters, specifically the *ABCC* subfamily. The *ABCC1* gene exhibits high expression in roots when exposed to As [53]. Phytochelatins and glutathione form complexes with As for subsequent sequestration in vacuoles through these transporters [49]. In *Arabidopsis*, *AtABCC1* and *AtABCC2* are recognized as vacuolar transporters for As-phytochelatin sequestration, as shown in Fig. 1 [54]. Additionally, the vacuolar phosphate transporter (*VPT1*), associated with phosphate storage, has been linked to As tolerance in *Arabidopsis*. Overexpression of *VPT1* contributes to higher levels of As accumulation in *Arabidopsis* roots [55]. On the other hand, *PvOCT4* (organic cation transporter) and *PvGSTF1* genes work in synergy by initially reducing As(V) to As(III) and subsequently transporting As(III) through plant vesicles [56–58].

3.2. Long-distance translocation of arsenic

The As translocation efficiency from the roots to the shoots plays a crucial role in determining the tolerance of plants to As and influences the accumulation capacity of As hyperaccumulators. *P. vittata* is recognized to highly translocate As (III) and As (V), with As (III) being the most predominant form through xylem tissue since its less complexation makes it an efficient tissue transport [64].

High expression of the *ACR3* gene in root cells facilitates As efflux, developing healthier roots (Fig. 1) [52]. Additionally, the heterologous expression of *PvACR3;2* in *Arabidopsis* increased root-to-shoot translocation of As (III), which was found localized in membrane cells. It was identified that combining with the knockout *y-ECS* (y-glutamyl-cysteine synthase) and *PCS1* (phytochelatins synthase) mutants show higher root-to-shoot translocation [65]. On the other hand, the overexpression of *OsPIP2;6* resulted in the accumulation of As (III) in shoots, attributed to its mobilization through the vascular tissue [66]. Furthermore, the *ABBCC7 gene* encoding transporter in *O. sativa* was identified as essential for the root-to-shoot translocation of As, specifically, highly expressed in xylem parenchyma cells. Similarly, high expression of *ABBCC7,* characterized to have specific activity for As (III)-PC complex efflux, was found in root cells of *Nicotiana benthamiana* under As stress [48].

Table 2
Classification of gene transporters involved in arsenic efflux and translocation in plants.

Gene ID	Gene Name	Category	Related As specie uptake	Source	Plant Tissue	Localization	Reference
MW447114	*PvACR3;2*	Arsenite efflux permeases	Arsenite	*Pteris vittata*	Root and shoot cells, xylem	Cell and tonoplast membrane	[59]
OM141483	*PvAsE1*	Arsenic efflux	Arsenite	*Pteris vittata*	Root cells	Cell membrane	[60]
Os03g0107300 At1g02260	*Lsi2*	Si efflux transporter	Arsenite	*Oryza sativa* *A. thaliana*	Root cells	Cell membrane	[30]
Os05g48040 LOC_107807968	*OsMATE2*	Multidrug and toxic compounds extrusion	Arsenite	*Oryza sativa* *Nicotiana tabacum*	Root cells	Cell membrane	[61]
At1g30400 At2g34660	*AtABCC1* *AtABCC2*	ATP-binding cassette	Arsenite	*A. thaliana*	Root and shoot cells	Cell and tonoplast membrane	[54]
At1g63010	*AtVPT1*	Vacuolar phosphate transporter	Arsenate	*A. thaliana*	Root cells	Tonoplast membrane	[55]
Os04g49900	*OsABCC7*	ATP-binding cassette	Arsenite-PC	*Oryza sativa*	Root cells	Xylem parenchyma cells	[48]
At1g30220 At4g16480	*AtINT2* *AtINT4*	Inositol transporters	Arsenite	*A. thaliana*	Shoot cells	Cell membrane	[62]
Os01g0142800	*OsPTR7*	Peptide transporter	Dimethylarsinate	*Oryza sativa*	Shoot cells	Cell membrane	[63]
At5g64410	*PvOCT4*	Cation transporter	Arsenite	*Pteris vittata*	–	Vesicle membrane	[57]

Cell membrane inositol transporters (*INTs*) have been related to As translocation. Knockdown of *AtINT2* and *AtINT4* genes reduced As (III) in phloem compared with control plants [62]. Likewise, it has been reported that the oligopeptide transporter family (OPT) in *O. sativa* is responsible for transporting phosphate and other metal substrates in the cytosolic direction, potentially facilitating the long-distance distribution of As [67]. For example, *OsPTR7,* a peptide transporter (*PTR*) encoding gene, was suggested to participate in the long-distance translocation of the organic As form dimethylarsinate (DMA) due the higher expression of this transporter in shoot cells when compared with root cells, identifying that plays a vital role in the translocation of As into xylem to shoot-cells when *OsPTR7* knockout showed decreased concentration of DMA [63].

Once inside the cell, As (V) can be reduced by enzymes like *HAC1* and *ACR*, while As (III) can be reduced via phytochelatins (PCs). As (III) can then be sequestered in vacuoles using *ABCC1/2* transporters or stored in vacuoles, with *ACR3;1* transporting As (III) and *VPT1* transporting As(V). Different transporters aid the movement of As species to upper plant cells in the xylem. *ABCC7* transporters facilitate the passage of reduced As (III)-PC complexes. At the same time, *ACR3*, *Lsi2, and PIP2;6* are involved in As (III) translocation; once in xylem tissue, As can be mobilized and transferred to other cells through *PTR7* transporters, allowing the movement of dimethylarsenate (DMAS) and inorganic As (III) (INTs).

4. Mechanisms for arsenic perception and signaling

Understanding the plant molecular mechanisms triggered by As uptake in root cells and their subsequent responses in other cells via signaling pathways is crucial for preemptively addressing As-induced stress. This process plays a vital role in facilitating early sensing of As presence and ensuring that plants are ready to cope with the detrimental impacts of As, particularly oxidative stress [19]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) encompass essential signaling pathways involving hydroxyl radicals, superoxide anions, and nitric oxide (NO) molecules, respectively. These pathways play a dual role in responding to As stress and influencing plant development while also serving as inducers of oxidative stress, as shown in Fig. 2 [68].

When *Arabidopsis* was subjected to As(V) exposure, it experienced nitro-oxidative stress, which impacted the activity of enzymes related to antioxidative defense, including S-nitrosoglutathione reductase, recognized as a pivotal enzyme in NO metabolism.

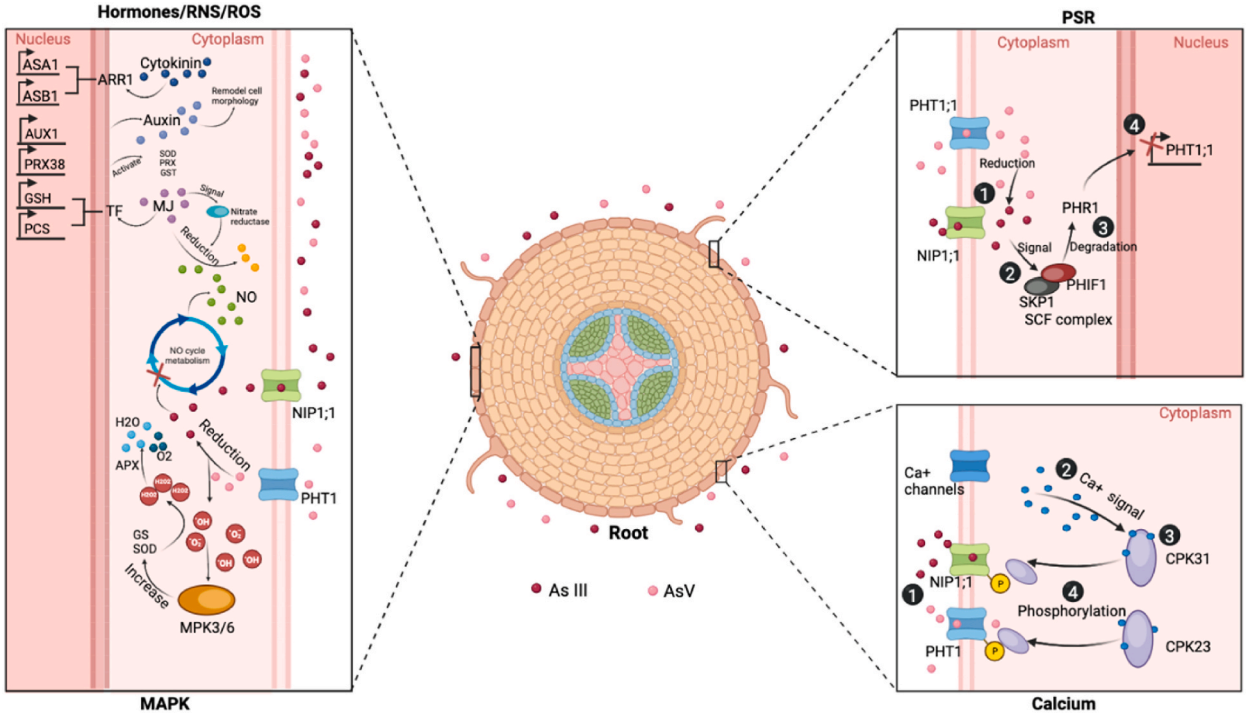

Fig. 2. Signal pathways activated in response to As(V) and As(III) perception in root cells. PSR (phosphate starvation) is activated in As (III) response via SCF (Skp, cullin, and F-box) complex, which degrades *PHR1* (Phosphate master regulator) and the subsequent repression of *PHT1;1* gene. Furthermore, the calcium signaling is activated in both As responses, binding to *CPK31* and *CPK23* to phosphorylate the membrane transporters *NIP1;1* and *PHT1*, respectively, and modulating the As uptake. Additionally, a hormone cascade is activated via cytokinin with the coordination of *ARR1* (*Arabidopsis* response regulator 1), allowing the transcription of *ASA1* and *ASB1* (Anthranilate synthases alpha and beta). Then there is enhanced expression of *AUX1* and *PRX3*8 that allows auxin response in root morphological remodeling and Methyl Jasmonate (MJ) that regulates the expression of PCS (phytochelatins) and GSH (glutathione) genes, also is involved as signal in the nitrate reductase activation that allows the reduction of NO (nitric oxide) accumulation due to the disruption of NO cycle metabolism by As(III). On the other hand, MAPK (mitogen-activated protein kinase) also is involved in response to ROS generation on As(V) reduction, MAPK3/6 increases SOD (superoxide dismutase), and GS (glutamine synthetase) that transform ROS into H_2O_2 (hydrogen peroxide) and then by APX (ascorbate peroxidase) reduces H_2O_2 to water.

Furthermore, it reduced the levels of molecules such as glutathione (GSH), with consequent repercussions on plant growth and lipid oxidation [69]. For instance, a transcriptomic analysis identified several genes upregulated in *O. sativa* under As treatment, including glutathione metabolism-related gene *Os09g0367700,* redox control genes; *Os06g0216000, Os07g0638300*, *Os01g0294500*, cell wall biogenesis genes; *Os05g0247800, Os11g0592000* and *Os03g0416200* and a protein-transport encoding gene *Os04g0524500* [70]. Additionally, indole-3-acetic acid (IAA) acts as a downstream signal for the NO-mediated reduction of As (V), playing a crucial role with NO as a signal molecule [71].

Likewise, As stress also induced changes in the distribution of peroxisomes in *Arabidopsis*. These organelles play a crucial role in signaling the redox balance during stress responses, which is associated with the levels of ROS and NO [72]. Additionally, As(V) was found to modulate the enzymatic activities within peroxisomes, including the inhibition of glycolate oxidase and hydroxypyruvate, as well as catalase inhibition promoting the formation of lateral roots in comparison to primary roots [68]. A previous study using RNA-seq analysis in *Arabidopsis* under As stress revealed genes in response to stress such as Catalase-encoding enzymes; *CAT1, CAT2,* and *CAT3* genes; heat-shock proteins encoding genes; *Hsp70-4* and *Hsp90-1* as well as proline biosynthesis-related genes; *P5CS1* and *P5CS2* in rosette leaves [73]. Further, ten differentially expressed *TaCAT* genes in *T. aestivum* under As stress were identified, which is related to reducing the excessive ROS produced by As exposure [74].

Additional molecular mechanisms triggered by As exposure encompasses the activation of genes associated with plant hormone signal transduction [75]. In this context, phytohormones serve as signal molecules that regulate various physiological processes, including auxin, cytokinin, ethylene, jasmonates, and brassinosteroids, as depicted in Fig. 2. For instance, in rice, the expression of the *OsAUX1* gene was observed in response to As perception [76]. The auxin signal generated by this gene plays a protective role by facilitating the remodeling of root morphology [68]. This adaptation is essential to counteract the detrimental impact of As on root growth [76]. Similarly, the *OsPRX38* auxin-catabolism-related gene, part of the class III peroxidases multigene family of plant-specific peroxidase, enhances As tolerance by activating stress-related mechanisms such as *SOD* (superoxide dismutase), *PRX* (peroxidase), *GST* (glutathione-*s*-transferase) activity promoting higher lignification in root cells, acting as a barrier to prevent the entry of As during As perception [77]. It has been reported that SNAC3 overexpression plays a pivotal role in boosting As stress tolerance and grain productivity in *O. sativa* by antioxidant enzymes, photosynthesis, and osmolyte accumulation [78].

Moreover, in *Arabidopsis*, cytokinins coordinate in signaling root growth under As conditions. This coordination is achieved by regulating type-B *Arabidopsis* response regulator 1 (*ARR1*), which stimulates the transcription of *ASA1* and *ASB1* genes, known as Anthranilate synthase alpha and beta subunits, respectively [79]. On the other hand, the hormone methyl jasmonate (MJ) is a significant regulator and signaling molecule in plants, capable of modulating the response to As stress [80]. MJ regulates the expression of genes related to glutathione (GSH) and phytochelatins (PCS), and it interacts with nitric oxide (NO). This interaction enhances antioxidant enzyme levels and nitrate reductase activity in *O. sativa*, *Brassica napus*, and lemongrass when treated with As(V). This regulatory action helps alleviate the oxidative damage induced by As. Additionally, MJ affects the expression of polyphenol oxidase and phenylalanine ammonia-lyase enzymes and the glutathione-ascorbate cycle [81–83].

Besides, the mitogen-activated protein kinase (MAPK) pathway becomes active upon perceiving As stress, initiating intracellular signaling responses [84]. This activation leads to the control of gene expression by transcription factors. For instance, under As stress, differential expression of rice MAPK genes, *OsMPK3* and *OsMPK6*, has been identified, and their overexpression results in increased transcription of genes involved in coping with ROS. These genes include superoxide dismutase, ascorbate peroxidase, and glutamine synthetase, enhancing the plant's response mechanisms to As stress [17]. Moreover, calcium signaling represents another cascade in the As stress response. In *Arabidopsis*, As(V) can induce a significant calcium signal [18]. Calcium-dependent protein Kinase 23 (*CPK23*) plays a crucial role in this process, as it interacts with *PHT1* (phosphate transporter), leading to the subsequent phosphorylation of *PHT1*. This regulation governs the perception and entry of As into the root cell [18]. On the other hand, *CPK31* interacts with *NIP1;1* to control As transport [85]. Furthermore, melatonin has been observed to interact with calcium, enhancing As tolerance in *Vicia faba*. This synergy between melatonin and calcium jointly suppresses cell death, DNA damage, and ROS production induced by As [86].

The analogy between arsenate (AsV) and phosphate (PO_4) allows As(V) to activate genes associated with the regulatory elements of the phosphate starvation response (PSR). This activation coordinates the cellular machinery for signaling detoxification pathways in response to As(V) [87]. Moreover, a sophisticated sensing mechanism governs As(V) uptake. This regulatory process involves the suppression of the *PHT1;1* transporter, orchestrated by the SCF complex, a molecular ensemble consisting of Skp (S-phase kinase-associated protein 1), cullin, and an F-box complex. Within this complex, an *SKP1-like* protein and *PHIF1* (PHR1-interactor F-box) collaborate to recognize the presence of As(V) as a signaling cue. Subsequently, this recognition triggers the degradation of *PHR1* (Phosphate starvation response master regulator). The degradation of *PHR1*, in turn, leads to the inhibition of the *PHT1;1* gene expression and reduction of As uptake [88].

5. Reduction and sequestration of arsenic in plants

As(V) is converted to As(III) within the plant system for further sequestration. This process can occur through As-related enzymes and non-specific As antioxidant metabolites [89]. For instance, the enzymatic response is carried out by an As(V) reductase encoded by the *ACR2* gene, with glutathione as an electron donor [90,91]. Additionally, in root meristematic cells, mitochondrial enzymes are involved in the conversion of As(V) to As(III) [89]. This transformation occurs within the chloroplast, involving cytochrome oxidase and a segment of the electron transport chain. However, this process is associated with an imbalance in energy and the production of ROS [90]. The High Arsenic Concentration 1 (*HAC1*) gene encodes an As(V) reductase, which converts As(V) into As (III), enabling the export of As(III) from roots, which restricts the translocation of As(V) to shoots as a detoxification route [92]. It is recognized that

reduction of As(V) to As(III) is needed for compartmentalization into vacuoles [88].

It was found that 30–40 % of the As(V) taken up by roots was converted to As(III) in *P. vittata* [64]. Likewise, it has been reported that during As(V) treatment in *Hydrilla verticillata* and *Phragmites stratiotes*, As(III) dominated the portion of As accumulation, and the activity of the As(V) reductase enzyme in both root and shoot tissues was significantly increased [93]. Notably, it was observed that *P. vittata*, *H. verticillata*, and *P. stratiotes* rapidly oxidized As(III) in roots when grown in As(V) medium [94].

As sequestration is a cellular mechanism designed to prevent and mitigate the adverse effects of As when it is present in the cytoplasm. It is a crucial coping strategy for plants since As cannot interact effectively with other biological macromolecules, including vital enzymes [95,96]. One form of sequestration involves the chelation of As by glutathione-based polypeptides known as phytochelatins (PCs) and glutathione, resulting in the sequestration of As(III) [13]. Specifically, As(III) has an affinity for the thiol groups found in these peptides. When As(III) is in the cytoplasm, PCs or GSH form a complex that is subsequently sequestered into vacuoles through the mediation of C-type ATP-binding cassette transporters (*ABCC*) [14]. The expression of PC synthase genes, such as *AtPCS1* in *Arabidopsis* facilitates the synthesis of PC*s*. Interestingly, the C-terminal portion of PCs plays a pivotal role in activating the enzyme, mediating the cellular response to As stress [97].

Furthermore, it has been observed that monothiol-As(V) exhibits more significant toxicity compared to the As(V) form but is less toxic than As(III). However, monothiol-As(V) demonstrates a higher rate of translocation from root to shoot, resulting in more toxic in *Arabidopsis* mutants of respective sequestration-related genes, phytochelatin (*cad1-3*), and glutathione biosynthesis (*cad2*) as well as phytochelatin transporters (*abcc12*), highlighting the involvement of this pathway in mediating As translocation [98]. Similarly, metallothioneins (MT) are a type of low-molecular cysteine-rich sulfhydryl proteins that exhibit a strong affinity for As(III) as a result of the presence of thiol groups, which facilitate the binding of As(III) [96]. The overexpression of the *MT2b* gene in *Arabidopsis* reduces As (III) levels in the roots, while an increase is observed in the shoots [15]. This finding suggests that *MT2b* may play a role in facilitating the transport of As from the roots to the shoots.

The ubiquitination process is a novel molecular mechanism identified in the As sequestration process. It is related to the protein breakdown pathway in plants that is regulated by the ubiquitin-proteasome system (UPS), which can be activated in response to various environmental challenges [99,100]. Hence, the process of ubiquitination, which involves the covalent binding of ubiquitin molecules to specific proteins within plant cells, is well recognized as a crucial mechanism for responding to As-induced stress in plants [99,101,102]. Furthermore, F-box proteins mediating protein ubiquitination in the SCF complex are essential for abiotic stress responses [100] and have also been reported to control Pi homeostasis [11]. An Arsenic Stress-Related F-box gene (*ASRF*) has been reported earlier by our group as a negative regulator of arsenic tolerance in *Arabidopsis* [103]. *ASRF* might function in a feedback loop to fine-tune the Pi equilibrium related to the phosphate starvation response caused by As-stress exposure. In addition, the *ARS5* mutant encoding a proteasome alpha subunit F1 protein (*PAF1*) of the 26S proteasome complex in *Arabidopsis* lines is involved in proteasome-mediated protein degradation related to As-response signaling and has been linked to an increased As tolerance [14].

Moreover, previous studies have reported a RING (Really fascinating New Gene) E3 ligase 2 in rice (*OsAIR2*) playing a role in the degradation of protein markers through the process of proteasome degradation [104]. The heterologous overexpression of *OsAIR2* into *Arabidopsis* resulted in enhanced seed germination and increased root length in the presence of As(V), indicating that the activity of ubiquitination serves as a beneficial post-translational regulatory mechanism for protein changes in response to As stress [104]. Furthermore, the introduction of exogenous RING E3 ligase-4 genes, namely *OsAIR4.1* and *OsAIR4.2*, into *Arabidopsis* plants resulted in enhanced resistance to arsenate (V) toxicity, as seen by increased seed viability, augmented root length, and overall improvement in plant growth [105]. Similarly, it was observed that there was a notable increase in the expression of RING E3 ligase 1 (*OsHIR1*) in rice when exposed to As. This overexpression of *OsHIR1* resulted in the degradation of the protein *OsTIP4;1*, located in the plasma membrane and associated with As uptake [106]. In a recent study, it was demonstrated that the process of SUMO (Small ubiquitin-like modifier) conjugation is implicated in the response to As and that the malfunctioning of the SUMO E3 ligase *SIZ1* in *Arabidopsis* mutants resulted in resistance to As (III) [107]. Consequently, it can be inferred that SUMOylation exerts a detrimental influence on plants in their defense against As(III). However, this effect is not observed in As(V) presence.

6. Arsenic extrusion mechanisms

In addition to regulating As transport, cells utilize mechanisms to actively remove As(V) and As(III) from their intracellular environments. These As extrusion mechanisms are vital for plant survival in As-contaminated soils [108]. The effectiveness of these mechanisms is dependent on the functioning of membrane transporters. In particular, the *ACR3* genes encode the As (III) antiporter membrane cell transporter, which has been recognized as a significant and efficient mechanism for the efflux of As (III) in *P. vittata* [59]. Moreover, previous studies have shown that the *PvACR3;2* gene derived from *P. vittata* has been successfully introduced into transgenic strains of *N. tabacum* and *Arabidopsis,* showing potential heterologous extrusion of As (III) in the root system [50,109]. Likewise, the *PvAsE1* gene, which has been classified as an *ACR3* gene, is situated inside the plasma membrane of *P. vittata*, facilitating the extrusion transport of As [60]. Accordingly, the orthologous transporter in *Marchantia polymorpha*, *MpACR3*, was characterized as a key extrusion mechanism, and the knockout of *MpACR3* showed high sensitivity to As [110,111].

Furthermore, the efflux of silicon is facilitated by the Si efflux transporter known as *Lsi2*, which also plays a role in the efflux of As (III). This transporter operates as a bidirectional transporter within the cell membrane, similar to aquaporins *NIP3;1*, *NIP;5*, and *NIP;6* that are present in *Arabidopsis*, rice, and *Lotus japonica*, respectively, which are mediated by the concentration gradient and permeability of the cell [30].

Heavy Metal Associated proteins (HMAs) possess a metal binding domain facilitating the homeostasis of metallic ions across cellular membranes and have been associated in response to As stress [112]. Their primary function is related to the detoxification

mechanism [113]. Specifically, the *OsHMA9* gene in rice has been identified as a metal efflux HMA protein that plays a crucial role in maintaining metal homeostasis. However, its specific function in the presence of As has not yet been fully elucidated [67]. The expression patterns of the Heavy Metal ATPase (HMA) family have been analyzed in *Cucurbita pepo* under As (V) stress [114]. The Cu/Ag clade members showed a positive modulation, especially *CpHMA6,* which exhibited high up-regulation in root and shoot tissues. *Arabidopsis* orthologous protein of this transporter was previously categorized as an ion pump transporting heavy metals [115]. Moreover, it has been observed that the expression of *OsMATE2*, which belongs to the MATE (multidrug and toxic compounds extrusion) family, is upregulated in rice during As exposure [116]. The heterologous expression of *OsMATE2* in Tobacco resulted in reduced translocation from the roots to the shoots, suggesting that it functions as an extrusion mechanism [61].

7. Arsenic hyperaccumulation

Hyperaccumulation is a characteristic observed in a limited number of plant species that exhibit high tolerance to As and can accumulate this metalloid in their aboveground tissues. These plants have been proposed in phytoremediation, phytomining applications, and fundamental investigations into the molecular mechanisms involved in As stress tolerance [60,117–120]. *P. vittata* is the first well-known As hyperaccumulating plant capable of accumulating up to 5000 mg As kg^{-1} [121]. To reveal the mechanism of As hyperaccumulation in *P. vittata,* translocation of radio-labeled As from roots to shoots due to a combination of increased root influx and decreased sequestration in roots, mainly when either exposure of As (III) or biotransformation of As (V) to As (III) occurs were observed [122]. For instance, *P. vittata* can concentrate 90–100% of As (V) in the roots and 93–98% of As (III) in the shoot from the total As [123].

The primary mechanism responsible for the high tolerance and bioaccumulation of As (III) in *P. vittata* is the sequestration of this compound in vacuoles [124,125]. This process involves expressing two genes, *PvHAC1* and *PvHAC2*, which encode As (V)-reductases. These genes are predominantly expressed in the rhizomes and fronds of the fern [121,126,127]. This knowledge is supported by the observed up-regulation of *PvHAC1* and *PvHAC2* in response to As (V) but not As (III) [127–129]. Although model plants like *Arabidopsis* possess similar As (V)-reductases such as *AtHAC1*, their ability to specifically reduce As is limited, resulting in an inability to accumulate significant As concentrations [91,130]. Furthermore, *PvACR2* and *PvACR3* encoding for an As (V)-reductase and As (III)--transporter, respectively, participates in the translocating and sequestering of As in shoot tissues [131]. The activation of the *ACR* gene has been associated with the conversion of As (V) to As (III), and the suppression of this gene has been demonstrated to result in the increased accumulation of As (V) in *Arabidopsis* [132]. Moreover, the up-regulation of genes such as *PvGAPC1* (Glyceraldehyde 3-Phosphate Dehydrogenase), *PvOCT4* (Organic Cation Transporter 4), and *PvGSTF1* (Glutathione S-Transferase) is associated with As tolerance and bioaccumulation [57]. Specifically, *PvGAPC1* exhibits a higher affinity for As (V) than phosphate, producing 1-arseno-3--phophoglycarate [56–58]. Additionally, it was observed that the suppression of *PvAse*, a well-defined gene responsible for encoding a plasma-membrane-orientated As (III) efflux protein, resulted in a decrease in the movement of As (III) from the root to the shoot tissues [60].

Besides, a transcriptomics analysis on *P. vittata* showed six distinct families of transporters related to As transport, including ACR3, ABC, P-type ATPase, MFS (Major facilitator superfamily), MIP, and nitrate transporter families [118]. Tonoplast proteomics further supported this finding, which validated the presence of 119 transporters, specifically, MIP, P-type ATPases, and ABC proteins are significant contributors to As compartmentalization [118]. Moreover, implementing strategies such as the selenium (selenate) treatment has demonstrated the potential to enhance As accumulation in *P. vittata*. This approach upregulates genes associated with As (V) uptake and reduction, including *PHT1;3, HAC1, ACR3*, and *PHT1*, leading to increased translocation and sequestration of As in the vacuoles of frond cells [133].

8. Epigenetic regulation of arsenic stress

Epigenetic regulation plays a pivotal role in plant responses to As stress, modulating gene expression without altering the underlying DNA sequence [134,135]. DNA methylation, a key epigenetic modification, has been shown to alter gene expression patterns in rice in response to heavy metals [136]. Hyper- and hypomethylation of DNA can lead to the repression or activation of stress-related genes. Erturk et al. [137] reported that DNA hypermethylation of some genes in germinating maize seeds exposed to low As levels. Likewise, it has been reported that DNA methylation is one of the molecular strategies employed by *Arundo donax* to counteract the cell abiotic stress caused by As pollution [138]. Moreover, it was reported that 5 mC (5-methylcytosine) content showed that accumulation of As was associated with affected DNA methylation in *Pteris cretica*, suggesting that As tolerance is strongly influenced by the methylation status of DNA [139].

Chromatin remodeling is another epigenetic mechanism that plants employ in response to As stress, enabling them to regulate gene expression by altering chromatin structure around stress-response genes [140]. It has been reported that ROS homeostasis and signaling mediate epigenetic mechanisms in heavy metal stress [141]. ROS may influence the activity of chromatin-remodeler enzymes by changing their post-translational modifications and, therefore, their activity [135]. Furthermore, plants can retain an 'epigenetic memory' of As exposure, which influences their stress responses and can be passed on to subsequent generations. Also, epigenetic memory may affect gene expression patterns in progeny in species such as *Arabidopsis* [142]. Transgenerational epigenetic inheritance, where stress-adaptive epigenetic marks are passed to future generations, has been observed in rice varieties, potentially influencing the expression of stress-responsive genes in offspring long after the stress has ceased [6,136].

Furthermore, small RNA pathways involving siRNAs and miRNAs contribute to gene silencing under stress conditions. Rice plants exposed to As(III) and As(V) showed varied miRNA expression. For instance, the down-regulation of Os-miR395 allowed the up-

regulation of a sulfate transporter (*Os03g09940*), indicating regulated sulfur homeostasis as a detox pathway in As stress [143]. In addition, 14 As (III)–responsive miRNAs, which regulate As transport in both roots and shoots, have been identified in rice. These miRNAs are associated with *PIP, TIP, ABC* transporters, and natural resistance-associated macrophage proteins (NRAMP) [144]. Likewise, it has been reported the *miR156j* family involvement in target function is related to stress-responsive *cis*-acting regulatory elements/motifs due to ROS generated by As(III) exposure [145]. Besides, Brassica plants exposed to As(V) showed organ-specific differences in microRNA expression. MiR159 and miR319 targeted genes such as MYB TF and oligopeptide transporter (*OPT1*), regulating signaling and biosynthesis of hormones such as gibberellin, ethylene, and jasmonates in response to As stress [146].

These findings underscore the complexity of plant responses to environmental stress and highlight the potential for using epigenetic mechanisms in developing crops with enhanced As stress tolerance. Nonetheless, further studies are needed to understand which enzymatic pathways or metabolic products are affected by epigenetic mechanisms in response to high As concentrations.

9. Opportunities for genome editing and genetic engineering

Genome editing and genetic engineering are promising for developing As tolerance in organisms, particularly plants. The precision of CRISPR/Cas9 technology enables targeted modifications to genes like phosphate transporters and nodulin 26-like intrinsic proteins, potentially reducing As uptake while preserving nutrient absorption [147,148]. The overexpression of genes responsible for chelating As, such as those involved in thiol compound synthesis, can be manipulated to enhance sequestration and reduce toxicity [149]. Approaches like gene silencing or knockout of specific transporters can significantly decrease As accumulation in plants [60].

Furthermore, transgenic approaches to introduce genes from As-tolerant species into more sensitive ones can confer increased

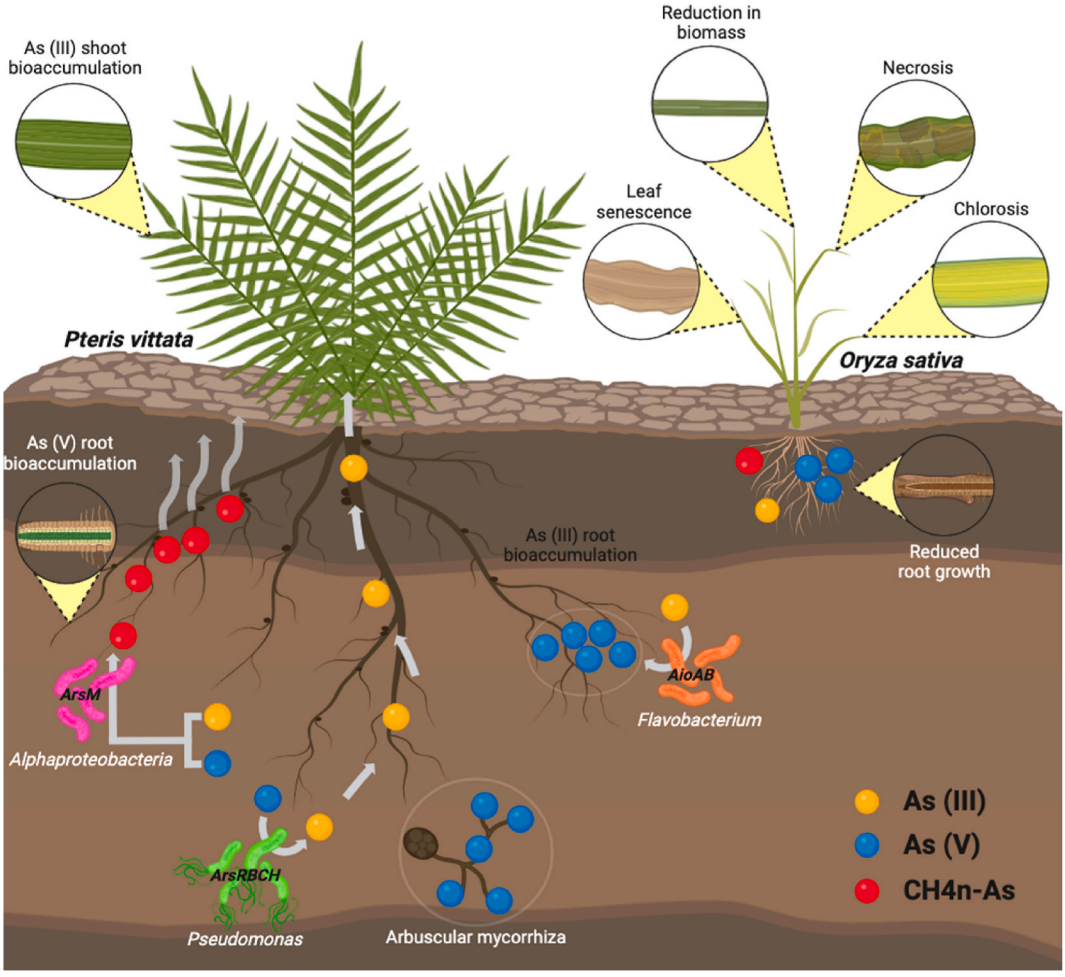

Fig. 3. Bioavailability of As mediated by microbial As-biotransformation mechanisms and As physiological damage. From left to right, there is the methylation of As by Alphaproteobacteria, followed by the sequestration of As by Arbuscular mycorrhiza and the reduction of As(V) to As(III) by *Pseudomonas*; and oxidation of As(III) to As(V) by *Flavobacterium* found in the rhizosphere. Once inside cell plants, physiological damage appears as leaf senescence, chlorosis, necrosis, and reduction biomass produced by As stress in almost all plants, such as rice. In contrast, hyper-accumulator plants, such as *P.vittata,* can modulate these symptoms and bioaccumulate in root and shoot cells As(V) and As(III), respectively.

resistance [150]. Synthetic biology tools can be important in devising new metabolic pathways to transform As into less harmful forms [151]. Modifying regulatory genes, such as transcription factors, can lead to coordinated expression of detoxification pathways, enhancing overall plant [70]. Strengthening the plant's antioxidant pathways and stress response systems can also provide broad-spectrum resilience against As [152]. Techniques involving non-coding RNAs offer sophisticated means to regulate As-responsive genes [145]. Gene stacking, where multiple tolerance traits are combined, may produce plants with robust resistance to As [153]. Finally, marker-assisted selection can identify and breed for As tolerance without direct genetic modification, using the knowledge of genetic markers linked to tolerance [32,154].

10. Role of microbiomes to mitigate arsenic stress

The plant microbiome, particularly the communities of bacteria and fungi associated with plant roots, plays a crucial role in the sequestration of As and the mitigation of As-induced stress in plants [155]. These microorganisms can transform As into less toxic forms through redox reactions and sequester As within their biomass, altering As availability and making it more or less accessible to the root system [156]. The As-specific transformation processes found in microorganisms can be classified as reduction of As(V) to As (III), oxidation of As(III) to As(V), and methylation of inorganic forms to n-methyl arsenicals [157,158]. In addition, the interaction between microbiome and plant can increase As tolerance via biotransformation mechanisms, as represented in Fig. 3 [159].

Bacteria and fungi have developed mechanisms to volatilize As by converting it into gaseous forms, a process that can help to remove As from contaminated sites [152]. Additionally, plant growth-promoting rhizobacteria (PGPR) can enhance plant growth and tolerance to As by producing siderophores that bind to As, phytohormones that stimulate growth, and enzymes that induce stress resistance [7]. The symbiotic relationship between mycorrhizal fungi and plant roots is another microbiome facet contributing to As stress mitigation. Mycorrhizae can increase As tolerance by enhancing nutrient uptake, improving water use efficiency, and directly immobilizing As in the soil [160]. Recently, it has been reported using axenically cultivable fungus *S. indica* in highly As-contaminated agricultural soil may reduce arsenic stress and accumulation in rice plants through modulation in iron (Fe) homeostasis [161]. Besides, the application of biochar, a charcoal-like substance made from biomass, can provide a habitat for beneficial microorganisms and adsorb As, thereby reducing its bioavailability to plants [162]. On the other hand, the cyanobacteria *Leptolyngbya* sp. XZMQ and plant growth-promoting bacteria *Bacillus* XZM regulate rhizosphere microbial structure, increasing the activity of nitrogen and carbon-fixing microorganisms expressing *arsC, arsM, aioA*, and *arrA* genes, which reduce the mobility and bioavailability of As in soil, and thereby reduce As absorption by root plants [163].

Furthermore, the enhancement of As phytoremediation potential by *P. vittata* can be achieved through the inoculation of *Alcaligenes* sp., which has been found to improve the reduction of As(V). This improvement has a favorable impact on the bioavailability and bioremediation effectiveness of the fern [164,165]. Moreover, the microbial abundance in *Brassica rapa* ssp., genotypes with high As accumulation differs from those with low As accumulation. While Patescibacteria, Acidobacteria, and Rokubacteria were less abundant in low-accumulators, *Flavobacterium* and *Sphingomonas* were more abundant in high-accumulators [166]. Similarly, rhizosphere interactions between *P. vitatta* and *Punica granatum* exhibited greater tolerance to As due to greater abundance of the members belonging to Alphaproteobacteria and Rhizobiales [56].

These microbiome-plant interactions are an important natural resource for developing sustainable strategies to manage As-contaminated environments. Leveraging the plant microbiome for bioremediation involves understanding and manipulating these complex biological interactions to enhance As sequestration and detoxification processes [167]. Integrating microbiome management with traditional phytoremediation techniques could lead to more efficient approaches to mitigate environmental As toxicity [168].

11. Conclusions

The field of plant genomics and epigenetics shows promise for understanding plant responses to As stress. Advances in genomic sequencing and editing technologies have identified numerous genetic elements associated with As uptake, signaling, transport, and sequestration. Yet, the dynamics of their interplay and regulatory networks remain to be fully elucidated. The transporters responsible for As translocation within phloem and xylem tissues and their regulatory mechanisms require further investigation. Decoding these signaling pathways could revolutionize phytoremediation and crop resilience. Furthermore, integrating genomics with epigenetic insights has the potential to reveal the regulatory mechanisms that control gene expression in the presence of As, shedding light on how plants not only survive but can adapt to high As environments. Harnessing cutting-edge genome engineering tools, such as CRISPR/Cas systems, could discover novel genes and alleles that confer As tolerance, translocation efficiency, and storage capacity. When used with epigenetic modification mapping, such genomic innovations could facilitate the development of plant varieties customized for As bioremediation. These varieties could be engineered for resistance or hyperaccumulation properties, offering a dual advantage in agricultural sustainability and environmental cleanup efforts.

Funding

This work was supported by the USDA - National Institute of Food and Agriculture grant number 2023-38821-39586.

Data availability statement

Data included in this paper are referenced.

CRediT authorship contribution statement

Celeste Gracia-Rodriguez: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Carlos Lopez-Ortiz:** Writing – review & editing, Writing – original draft, Supervision, Investigation. **Gerardo Flores-Iga:** Writing – original draft, Investigation. **Lizbeth Ibarra-Muñoz:** Investigation. **Padma Nimmakayala:** Project administration, Funding acquisition. **Umesh K. Reddy:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Nagamani Balagurusamy:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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