

Review

# Arsenic-Induced Oxidative Stress and Antioxidant Defense in Plants

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**Abstract:** The non-essential metalloid arsenic (As) is widely distributed in soil and underground water of many countries. Arsenic contamination is a concern because it creates threat to food security in terms of crop productivity and food safety. Plants exposed to As show morpho-physiological, growth and developmental disorder which altogether result in loss of productivity. At physiological level, As-induced altered biochemistry in chloroplast, mitochondria, peroxisome, endoplasmic reticulum, cell wall, plasma membrane causes reactive oxygen species (ROS) overgeneration which damage cell through disintegrating the structure of lipids, proteins, and DNA. Therefore, plants tolerance to ROS-induced oxidative stress is a vital strategy for enhancing As tolerance in plants. Plants having enhanced antioxidant defense system show greater tolerance to As toxicity. Depending upon plant diversity (As hyperaccumulator/non-hyperaccumulator or As tolerant/susceptible) the mechanisms of As accumulation, absorption or toxicity response may differ. There can be various crop management practices such as exogenous application of nutrients, hormones, antioxidants, osmolytes, signaling molecules, different chelating agents, microbial inoculants, organic amendments etc. can be effective against As toxicity in plants. There is information gap in understanding the mechanism of As-induced response (damage or tolerance response) in plants. This review presents the mechanism of As uptake and accumulation in plants, physiological responses under As stress, As-induced ROS generation and antioxidant defense system response, various approaches for enhancing As tolerance in plants from the available literatures which will make understanding the to date knowledge, knowledge gap and future guideline to be worked out for the development of As tolerant plant cultivars.

**Keywords:** abiotic stress; environmental pollution; metalloids; metal transporter; xenobiotics; reactive oxygen species

## 1. Introduction

Arsenic (As) is an environmental non-essential metalloid that poses a severe risk to all forms of plant and animal life [1,2]. It is a naturally occurring 20th most plentiful and widely distributed element on the planet. At present, more than 2.5 billion people on the earth depend on groundwater, and contamination of groundwater by As-tainted toxicity has

become a serious concern [3]. Contamination of As in groundwater is increasing daily and it is estimated that 500 million people round the globe will be affected by As contamination. This metalloid enters into the ecosystem via natural activities such as weathering and mineralization of earth crust and also by anthropogenic activities that include application of As-based pesticides, insecticides, fertilization with municipal solid wastes, and irrigation with As-tainted groundwater [4]. Thus, animals and humans are irradiated to As directly through the consumption of As-tainted water or indirectly by ingestion of foods from the ecosystem. It is well-known that food chain is affected by As when agricultural products become contaminated [5].

Plants exhibit morphological and physio-biochemical disorders due to As toxicity. It has been reported that root proliferation and extension are inhibited by As because root is the foremost organ to be subjected to As [6]. Arsenic contamination reduces nodule formation in roots and shows wilting, curling, and necrosis of leaf blades. Arsenic toxicity hampers plant growth by decreasing cell proliferation and biomass buildup. Arsenic binds to enzymes and proteins, impairing cell biochemistry and disrupting physiological processes like photosynthesis, respiration, transpiration in plants [4]. It can deplete plants reproductive capacity, obstructing photosynthetic processes and resulting in decreased plant growth and yield [7,8].

Reactive oxygen species (ROS) are continuously evolved by plants under stress conditions and generate oxidative stress which adversely affects different cell components like lipids, proteins, and DNA [9,10]. Higher level of As(III) and As(V) exposure promotes the accumulation of ROS in plants and those play role in the translation of As(V) into As(III) [11,12]. Arsenic toxicity enhances lipid peroxidation that damages cellular membranes by electrolyte leakage (El, [13]).

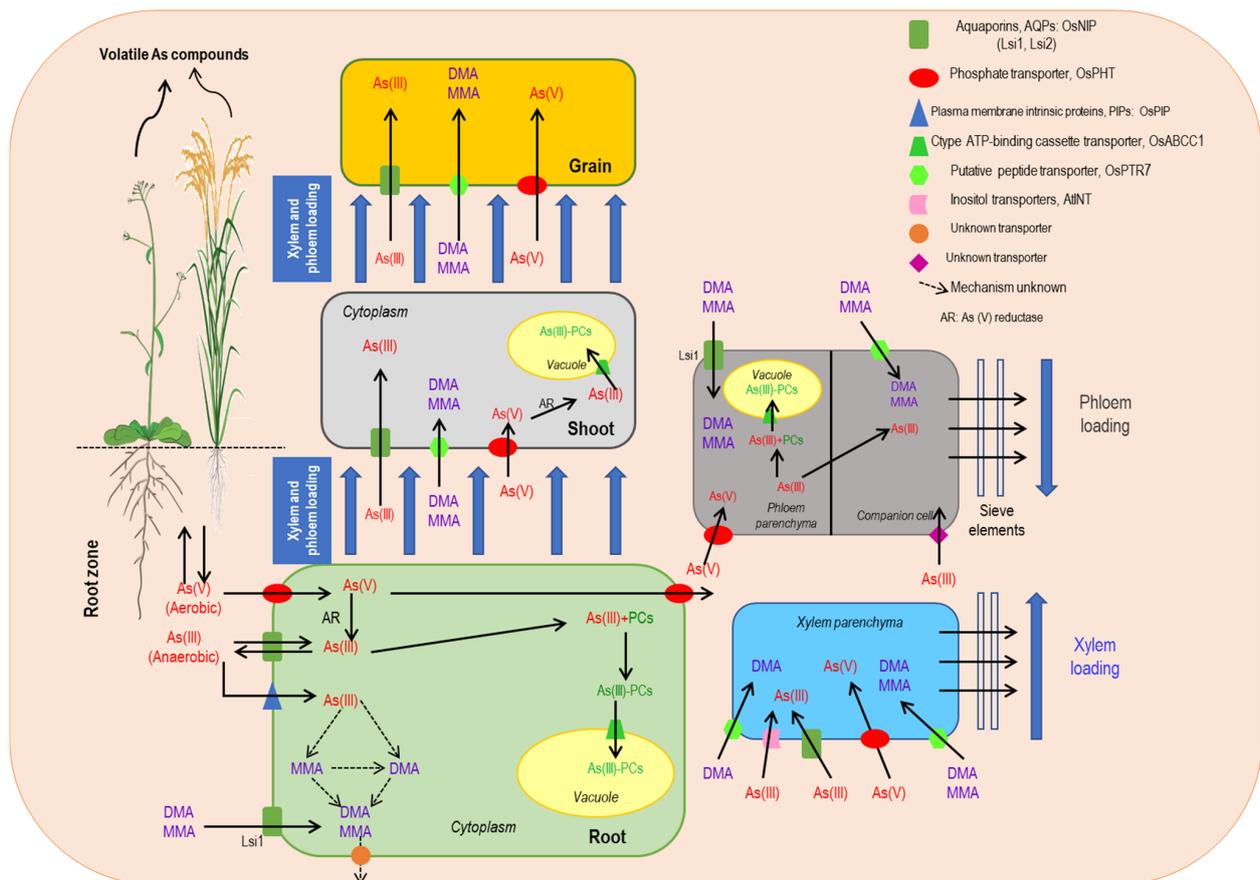
Plant continuously fostered robust machineries to fight against injurious effects of ROS by using enzymatic antioxidants including, superoxide dismutase (SOD), catalase (CAT), ascorbate peroxidase (APX), glutathione reductase (GR), monodehydroascorbate reductase (MDHAR), dehydroascorbate reductase (DHAR), glutathione peroxidase (GPX), glutathione S-transferase (GST), and non-enzymatic antioxidants including, ascorbic acid (AsA), glutathione (GSH), tocopherol, phenolic acids, carotenoids, non-protein amino acids etc. Antioxidant enzyme activities are key players for scavenging ROS directly or indirectly from stressed cells [14]. A steady-state balance is maintained in plant cells, the antioxidant defense system, and ROS buildup. Besides, an optimal ROS level in the plant cells allows for appropriate redox biology reactions and aid in the adjustment of variety of activities required for plant growth progressions [10,15,16]. Literature describes that As stress directs to oxidative stress and promotes functions of antioxidant enzyme to counteract this stress in rice [17,18].

Although many reports are available on the mechanisms of As accumulation, absorption, and toxicity in plants, the information regarding As-provoked oxidative stress and antioxidant defense mechanisms are still inadequately recognized in plants. Therefore, this article discusses the mechanisms of As-induced oxidative stress and the involvement of antioxidant defense systems in detoxification of As-stimulated oxidative injury in plants.

## 2. Arsenic Uptake and Accumulation in Plants

In soil, organic As compounds remain in addition to inorganic As. The inorganic and organic both forms of As in soil can be uptaken by plants while the higher rate and part is the inorganic As. Arsenate [As(V)]/AsO<sub>4</sub><sup>3-</sup> and arsenite [As(III)]/AsO<sub>3</sub><sup>3-</sup> are the inorganic entities. Generally inorganic forms, As(III) and As(V) are more toxic than the organic form. Aerobic soil predominates the generation of As(V) and anaerobic/inundated soil is predominated by the occurrence of As(III) [19]. Methylated As [monomethylarsinic acid (CH<sub>3</sub>AsO(OH)<sub>2</sub>; MMA) along with dimethylarsinic acid ((CH<sub>3</sub>)<sub>2</sub>AsOOH); DMA] are commonly demonstrated organic As compound. Microorganisms are involved in conversion of As(V)/As(III) to MMA and DMA by distinct pathway. It is very usual that root is the first organ through which As enters the plants but As can enter through all the

submerged parts of plants [20]. After crossing the root epidermis and passing through the apoplastic and symplastic pathways, As enters the xylem or phloem through which bulk flow of As occurs and can be distributed to different plant organs including stem, leaf, reproductive parts and even seeds. However, cell wall, especially the membrane plays pivotal responsibility for controlling the rate and amount of As transport though it is variable among As accumulators and non-accumulators. Plant's root/membrane selective transporters and pathways are concerned for the entrance, uptake and translocation of inorganic and organic As [21]. A schematic illustration of As uptake and accumulation in plants has been presented in Figure 1.



**Figure 1.** Schematic illustration of As uptake, translocation, accumulation and detoxification in plants. The dotted arrows indicate that the pathways/mechanism are not known properly. MMA: monomethylarsinic acid  $[(\text{CH}_3\text{AsO}(\text{OH})_2)]$ ; DMA: dimethylarsinic acid  $[(\text{CH}_3)_2\text{AsOOH}]$ ; nodulin 26-like intrinsic proteins (NIPs) which are as a group recognized as aquaporin channels (AQPs: OsNIP); OsPHT: phosphate transporter; PIPs: plasma membrane intrinsic proteins (OsPIP); OsABCC1: C type ATP-binding cassette transporter; OsPTR7: putative peptide transporter; AtINT: inositol transporters; AR: As (V) reductase. As (V) can be entered to the root through OsPHT. As (III) can be entered or to be excreted through AQPs/OsNIP. As (V) can be converted into As (III) by the activity of AR. As (III) can be bound to GSH to form PCs complex and sequestered into vacuole. As (III) can also be converted into organic DMA and MMA (but the mechanism is not known clearly), both of the organic forms can be excreted outside the cell through unknown transporter. DMA and MMA can also enter the cell through AQPs/OsNIP. The AQPs/OsNIP, OsPHT and OsPTR7 have been assumed to be the transporter of various As species [As(III)/As(V)/MMA/DMA] towards the shoot and grain. Some of the As can also be released to the atmosphere as volatile As compounds.

Arsenite  $[\text{As}(\text{III})/\text{AsO}_3^{3-}]$  mainly enters through the root nodulin 26-like intrinsic proteins (NIPs) and these are as a group recognized as aquaporin channels (AQPs) in

together. Expression of OsNIP2;1 (Lsi1), in rice (*Oryza sativa*) root were reported in distant part of the plasma membrane in the zone of Casparian strips. OsNIP2;1 (Lsi1) regulates the influx of silicic acid ( $\text{Si}(\text{OH})_4$ ) and As(III) [22]. Another aquaporin channel OsNIP2;2 (Lsi2) is also found in plasma membrane of cells in both exodermis and endodermis of *O. sativa* root. These are  $\text{Si}(\text{OH})_4$  efflux transporters. Here, Lsi2 is restricted to the proximal side cell [23]. Influx of  $\text{Si}(\text{OH})_4$  as well as As(III) occur through Lsi1 whereas efflux of  $\text{Si}(\text{OH})_4$  occur through Lsi2; this process hinders As(III) entrance [22]. As(III) entrance in a number of plant species is bi-directional and is regulated by concentration difference. Similar mechanism was noticed in different plants like *Pteris vittata*, *Lotus japonicas* and *Arabidopsis thaliana* [24–26].

Plasma membrane intrinsic proteins (PIPs), such as OsPIP2;4, OsPIP2;6 and OsPIP2;7 can also control As(III) entrance but the mechanism is still ambiguous [27]. When As is present attaching the root zone, it can enter the root or efflux from the root or because of its affinity it can be bound to GSH as well as its derivatives phytochelatins (PCs) [28]. Once forming the As(III)-PCs it is sequestered in vacuole mediated by C-type ATP-binding cassette transporter (OsABCC1) [29].

Arsenate  $[\text{As}(\text{V})]/\text{AsO}_4^{3-}$  is the most common form of As under aerobic and dry condition and structurally it is resembled to  $\text{PO}_4^{3-}$ ; this is the cause for using the same transporter/pathway by both species [21].  $\text{PO}_4^{3-}$  transporter genes (OsPHTs) were recognized and phosphate transporter, OsPHT1;8 (OsPT8) and OsPHT1;1 showed high affinity for  $\text{PO}_4^{3-}$  and As(V) in *O. sativa* L. [30]. However, after uptaking As(V), it is quickly converted into As(III) where As(V) reductase (AR) activity is involved. There are two As (V) reductases, OsHAC1;1 and OsHAC1;2 in the root of *O. sativa* [31]. This converted As (III) can be released outside of the root through efflux or it can be converted into As(III)-PC complexes; mechanism of the both has been discussed in the previous part of this section.

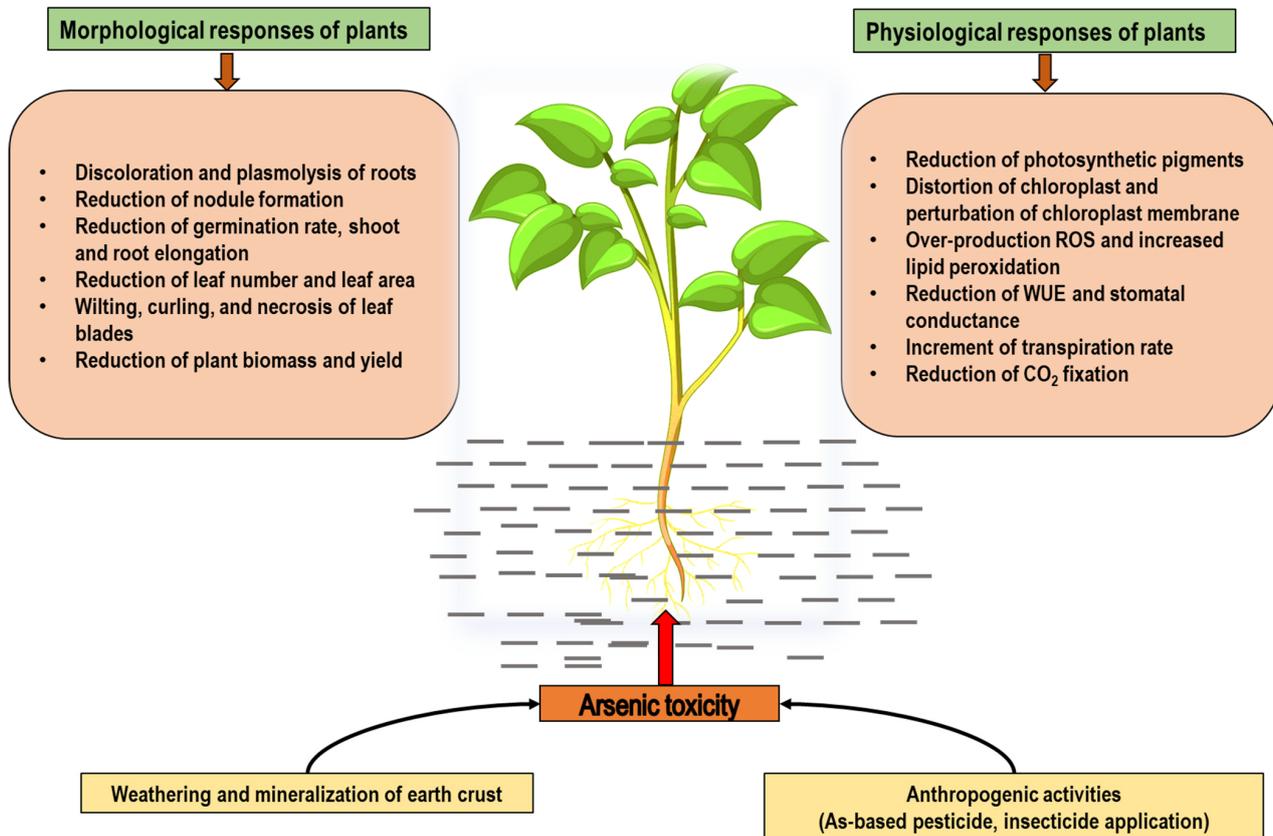
Aquaporin Lsi1 has been proposed to be involved in entrance of MMA(V) as well as DMA(V) in *O. sativa* [32]. So, Lsi1 is involved in both the inorganic As (III) in addition to organic As transportation. Occurrence of MMA(V)-thiol complexes were also documented [33] whereas little is known about DMA(V) and it needs further study.

Arsenic transfer from root to other vegetative parts and to reproductive parts has been studied, moreover described in few reports which are mostly on *O. sativa* L. As(III) is more quickly taken up by root than the other organic species of As. OsNIP2;1 (Lsi1) is accountable for As(III) entrance, and Lsi2 is for As(III) efflux from root to xylem as reported in *O. sativa* L. [34]. Lsi1 and Lsi2 work sequentially or together for controlling the root entrance of Si along with As(III). Besides, Lsi1, Lsi2 and Lsi6 transpiration pool is also vital to manage As uptake [35]. In *O. sativa*, various Pi transporter genes (OsPT) have been reported which transport P and As(V) towards the root; some of which are OsPT1, OsPT2, OsPT4, OsPT6 [36]. AsV in converted to As(III) within root, after that it can enter the xylem via Lsi 2 [37]. The organic DMA as well as MMA cross aquaporin channels [38]. The DMA is tremendously mobile all through the vascular tissues; it can be transported very quickly from root to shoot and from leaves to seed in *O. sativa*. In *O. sativa* L. grain, As(III) is mainly translocated via phloem whereas DMA is translocated via both kinds of vascular tissues. A putative peptide transporter, OsPTR7 functions for in the long-distance transportation and accumulation of DMA [39]. Also, inositol transporters, AtINT2 and AtINT4 may function for the entrance of As(III) to phloem and its translocation into grain.

### 3. Arsenic Toxicity in Plants

Many studies reported that As availability in the soil can hamper the morphological and physio-biochemical functioning of plants consequently reducing crop yield (Figure 2); [2,40–42]. For instance, plants exposed to As showed discoloration, lignification, and plasmolysis of root cells which resulted in stunted plant growth [43]. In addition, As contamination severely reduced germination percentage, shoot and root elongation, root and leaf biomass, and seed vigor index of different plants [44–46]. Likewise, As exposure has been shown to reduce the leaf numbers, area of leaf, height of plant, and fresh and

dry biomass of plants [47,48]. Reduced biomass in the presence of As was possibly an outcome of enhanced permeability of the cell membranes, consequently increased leakage of cellular constituents/basic nutrients essentially required for energy generation, and optimum growth and development of plants [49].



**Figure 2.** Arsenic-induced morphological and physiological responses of plants.

Arsenic stress regulates water relation in plants [1,50]. For example, As stress reduced relative water content in wheat and pea plants [51,52]. Likewise, As stress in lettuce reduced water use efficiency (WUE), stomatal conductance, and increased plant transpiration rate [53]. In *Hydrilla verticillata*, As exposure reduced WUE and increased transpiration rate [54]. The As stress may disrupt the cell wall structure in leaves, resulting in decreased leaf water content.

Many studies described that As stress inhibited the activities of photosynthetic machineries in plants [50,55]. Arsenic toxicity causes decrease in the synthesis of photosynthetic pigments, distortion of chloroplast, and reduction of photosystem I (PSI) and photosystem II (PSII) activities [56]. Several plants such as *Zea mays*, *Trifolium pratense*, and *Lactuca sativa* decreased biosynthesis of chlorophyll (Chl) due to As stress [57–59]. In chickpea (*Cicer arietinum*) plants, As toxicity reduced Chl contents and consequently resulted in chloroplast distortion [60]. In soybean, As stress reduced the efficacy of PSII, stomatal conductance, and rate of photosynthesis [61]. Arsenic stress reduced Chl fluorescence and photosynthetic rate in *P. cretica* and *Spinacia oleracea* [42]. Arsenic-induced reduction in Chl content may be due to the reduction in ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCO) activity and degrading biosynthetic enzymes,  $\delta$ -aminolevulinic acid dehydratase and protochlorophyllide reductase [62]. It has been reported that As toxicity initiates disruption of microtubules that hampers the formation of stomata which results in abnormal stomata [63]. Arsenic stress triggers phosphatidic acid (PA) signaling and that PA involved in stomatal closure of soybean [64]. Arsenic-induced injurious effects on roots

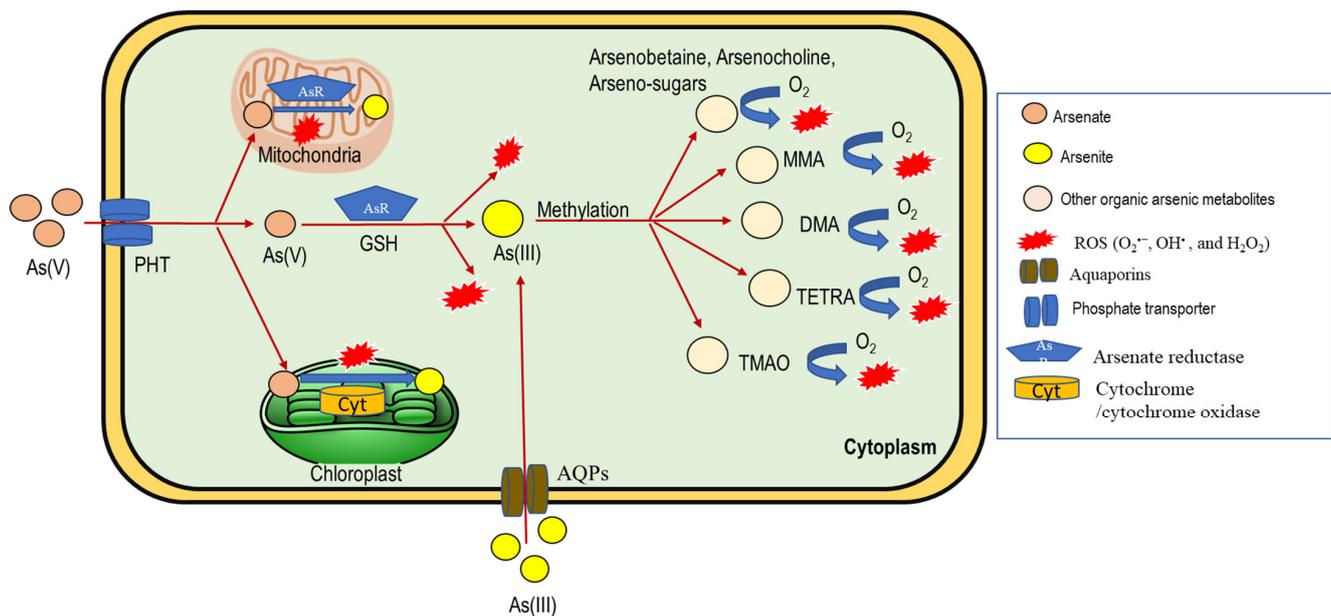
may affect the uptake of water and ions, which consequently, reduces the photosynthetic and transpiration rate and inhibits stomatal regulation [65,66].

Arsenic toxicity damages cell membranes and it is well-known that chloroplast membranes are quite sensitive to As-induced damages [2]. Arsenic-stressed *P. vittata* and *Leucaena leucocephala* leaves showed abnormal internal membranes of chloroplasts [67,68]. Literature shows that As stress led to perturbations in the chloroplast membranes organizations such as thylakoid membrane rupture and swelling [5]. In addition, Upadhyaya et al. [69] reported that As toxicity distorted chloroplast membrane and reduced carotenoids. Arsenic toxicity-induced dilapidation of chloroplasts and modification in its interior membranes, which adversely affect the photosynthetic pigments and the rate of carbon assimilation. Arsenic negatively affects the Chl *a* content and Chl *b* content, maximal photochemical efficiency of PSII ( $F_v/F_m$ ), the actual PSII photochemical efficiency ( $\Phi_{PSII}$ ), the quantum yield of CO<sub>2</sub> assimilation ( $\Phi_{CO_2}$ ), and the non-photochemical quenching (NPQ), net photosynthesis rate (*A*), stomatal conductance to water vapor ( $g_s$ ) and internal CO<sub>2</sub> concentration (*C<sub>i</sub>*) in *Pistia stratiotes* L. plants. The final result of As toxicity was lowered starch concentration, sucrose concentration, and glucose concentration in *P. stratiotes* [70].

Overall, As toxicity hampers crop growth by altering root plasmolysis, reducing photosynthetic attributes such as degradation of pigments, reduction of the rate of CO<sub>2</sub> fixation, reduction of stomatal conductance, and distortion of cell membranes integrity.

#### 4. Arsenic Toxicity and ROS Generation in Plants

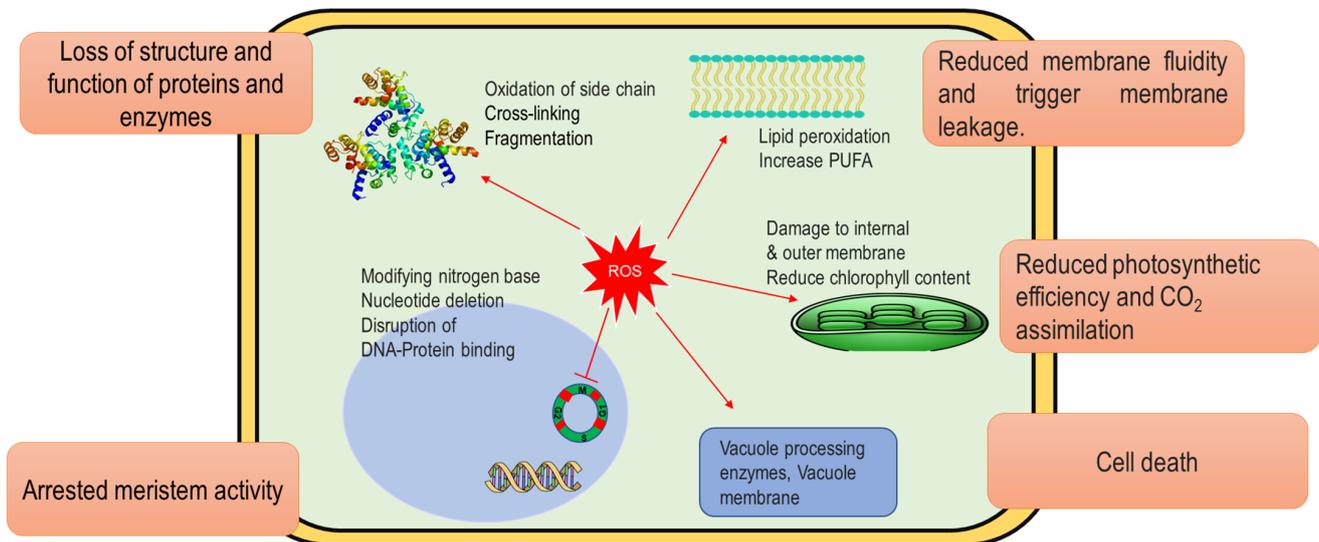
ROS generation is a common response in abiotic and biotic stresses [10]. ROS overproduction impaired plant health under stress by adversely affecting range of physiological process including lipid metabolism, DNA, photosynthesis, respiration, enzyme deactivation and growth retardation [71]. Several studies demonstrated As(III) and As(V) induce generation of ROS *viz.* superoxide ( $O_2^{\bullet-}$ ), the hydroxyl radical ( $OH^{\bullet}$ ), and H<sub>2</sub>O<sub>2</sub> [72,73]. As(III) is more detrimental to plant growth and generate more  $O_2^{\bullet-}$  than As(V), which generate more H<sub>2</sub>O<sub>2</sub> [74]. Although root cells sense first As, though generation of ROS started in leaves well before the As accumulation in the leaves tissues, suggested that root cells communicate As toxicity to leaves, probably by H<sub>2</sub>O<sub>2</sub> [75]. Under aerobic condition, As(V) is the main form which enter plant roots by phosphate transporter and within the cell it transform into As(III), which is the main source of ROS generation (Figure 3); [76]. The conversion of As(V) into As(III) is both, enzymatic and nonenzymatic [4]. Enzymatic reaction mediated by arsenate reductase (glutaredoxin) where GSH acts as electron donor [77]. This reduction is followed by methylation process and produces MMA, DMA, tetramethylarsonium ion (TETRA) and trimethylarsonium oxide (TMAO), arsenocholine, arsenobetaine and arseno-sugars [78]. These methylated products react directly with molecular oxygen and produce ROS. Non enzymatic reduction of As(V) into As(III) occurs through GSH [79]. This conversion, further causes severe oxidative stress as As(III) bind and consume GSH, and impairs antioxidant system. In chloroplast, As(V) is reduced into As(III) by cytochrome/cytochrome oxidase, disturbed electron transport chain and generated ROS [40,70]. In root meristematic cells, mitochondrial arsenate reductase is also found and transforms As(V) into As(III) [80].



**Figure 3.** Schematic overview of ROS generation in plant cell under As-stress. Phosphate transporter (PHT) and aquaporins (AQPs) facilitate entry of As(V) and As(III), respectively, into the cell. Initial ROS burst occurs due to arsenate reductase (AsR) mediated and non-enzymatic transformation of As(V) into As(III) in cytoplasm, chloroplast and mitochondria. Subsequently, a second sequential ROS burst occurs due to methylation of As (III) into other organic arsenic metabolites viz. monomethylarsinic acid (MMA), dimethylarsinic acid (DMA), tetraethylarsonium ion oxide (TETRA), trimethylarsonium oxide (TMAO), arsenobetaine, arsenochlorine and arsenosugars.

Lipid peroxidation, a common toxic effect of As induced ROS, also observed in hyperaccumulating *P. vittata* [13], hampered cellular and membrane functions [81]. Lipid peroxidation due to ROS is mostly monitored as malondialdehyde (MDA) content, a main product of lipid peroxidation, along with membrane leakage [11,82]. Overproduction of ROS increases polyunsaturated fatty acid (PUFA) and reduces saturated fatty acid of membrane lipids and membrane fluidity, thereby increases membrane leakage [72,83]. ROS also affects enzyme and protein structure and activity by oxidation of side chains, cross-linking and inducing fragmentation of backbone [5,84]. ROS generation under As-stress also modifies nitrogenase base, nucleotide deletion, disrupts protein-DNA binding and may lead DNA cracks [85,86] (Figure 4). In *Pisum sativum*, chromosome or microtubule damage has been reported under As stress which restricted root meristem activity [87]. Restricted root growth under As-stress may attribute to ROS-induced arrest of mitotic division due to down regulation of cell cycle genes and slow progression of G1 to G2 and from S to M stage, and decreases mitotic index (number of cells progressing into mitosis to the total number of cells) [88,89]. Root growth is also restricted due to root tip death. ROS induces programmed cell death by affecting vacuolar processing enzymes, signaling and triggers programmed cell death [90]. As toxicity caused asymmetric distribution of peroxisomes in *A. thaliana* root cells and a greater number of peroxisomes occurs in root meristematic zone as compared to root differentiation zone, and the higher peroxisomal ROS generation at root tip induces programmed cell death [91]. The differences in peroxisomal number may be due to As-induced pexophagy, a selective autophagy of peroxisomes [92]. Though it seems roots may have strong antioxidant defense against As toxicity than leaves [46], growing evidence suggested that root gravitropism, cell death, stomatal regulation and other growth and developmental response, under varied abiotic stresses are results of interplay between ROS and phytohormones [93,94]. The ROS and hormonal interplay control gene expression and induce stress responses. As stress upregulated abscisic acid, ethylene and jasmonic acid signaling [95]. ROS generated in chloroplast and mitochondria disrupt ETC by damaging internal and outer membranes of chloroplast and mitochondria [70]. The disruption of

chloroplast membrane reduced photosynthetic pigment and carbon fixation [68,96]. Even, chloroplast membrane of old leaves of As hyperaccumulator, *P. vittata* was also disrupted with high accumulation of As [67].



**Figure 4.** Detrimental effects of reactive oxygen species on cellular component and their consequences (rectangle box, outside the cell) under arsenic stress.

### 5. Arsenic-Induced Oxidative Stress in Plants

Arsenic accumulation in plant tissue generates oxidative stress, mainly during detoxification into less toxic metabolites and disruption of electron transport chain in chloroplast and mitochondria. Oxidative stress was accessed in diverse group of plants (Table 1) under As-stress. Rice, a hyperaccumulating species, also exhibited enhanced  $H_2O_2$  and thiobarbituric acid reactive substance (TBARS) content when seedlings were subjected to  $50 \mu M$  As-stress up to 30 days [97]. Arikan et al. [98] also observed similar higher  $H_2O_2$  and TBARS content in 14-day-old *Z. mays* seedlings under hydroponic condition with  $100 \mu M$  As(V). Alshahli et al. [99] observed 69% EL from *P. sativum* tissues under As-stress ( $NaAsO_2$ ;  $20 \mu M$ ) as compared to only 10% EL from non-stress control condition. Annual and perennial ryegrass when supplied  $NaAsO_2$  ( $2.51 \text{ mg mL}^{-1}$ ) both exhibited marked increase in  $O_2^{\bullet-}$  content in mature, expanded and emerging leaves at 60 days, and the content reached up to 65% in emerging leave of annual ryegrass [100]. Similarly, when soybean seedling experienced As stress ( $NaAsO_2$ , 10 and  $100 \mu M$ ), ROS viz.  $O_2^{\bullet-}$ ,  $OH^{\bullet}$  and  $H_2O_2$  remarkably increased within 5 days and due to this ROS burst, LOX activity also enhanced [5].

**Table 1.** Oxidative stress in different plant species under arsenic stress.

Plant Species	Arsenic Levels and Growth Condition	Stress Period	Major Effects	Reference
<i>Oryza sativa</i> Japonica type	$As_2O_3$ ; 10, 20, 30, 40 and $50 \mu M$ ; mixture of soil, perlite and vermicompost	30 days from sowing	$H_2O_2$ and TBARS increased under As stress in dose dependent manner and reach up to 1.93 folds and 1.71-folds in $50 \mu M$ As, as compared to control.	[97]
<i>Zea mays</i> cv. DKC5741	$Na_2HAsO_4 \cdot 7H_2O$ ; $100 \mu M$ ; hydroponic	14 days	11% $H_2O_2$ and 61% TBARS content increased with As-stress over control.	[98]

Table 1. Cont.

Plant Species	Arsenic Levels and Growth Condition	Stress Period	Major Effects	Reference
<i>Pisum sativum</i>	NaAsO <sub>2</sub> ; 20 µM; mixture of sand, perlite and pit; Hoagland solution	40 days	74 and 63% higher content of H <sub>2</sub> O <sub>2</sub> and MDA was obtained as compared to control. Increased electrolyte leakage (69%) was observed over control (11%). Increased H <sub>2</sub> O <sub>2</sub> content by 44% and 32% in expanded leaves of perennial cultivar (Mathilde) and annual cultivar (Idyll).	[99]
<i>Lolium perenne</i> cv. Mathilde, <i>L. multiflorum</i> cv. Idyll	NaAsO <sub>2</sub> ; 2.51 mg mL <sup>-1</sup> ; soil	60 days	In mature, expanded and emerging leaves of perennial ryegrass, superoxide anion (O <sub>2</sub> <sup>-</sup> ) increased by 26, 29 and 47%, respectively. While in annual ryegrass, mature, expanded and emerging leaves of annual ryegrass 30, 5 and 65% respectively, higher O <sub>2</sub> <sup>•-</sup> . Leaf H <sub>2</sub> O <sub>2</sub> and MDA content increased by 242 and 272% over control.	[100]
<i>Solanum lycopersicum</i> cv. SC 2121	Na <sub>2</sub> HAsO <sub>4</sub> ·7H <sub>2</sub> O; 50 µM; hydroponic	10 days	Activity of LOX in leaf enhanced by 127%. EL increased by 325% over control. Increase H <sub>2</sub> O <sub>2</sub> in roots by 32% and 65% in dose dependent manner while in leaves it was reduced over control.	[101]
<i>Spinacia oleracea</i>	25 µM and 125 µM As, NaAsO <sub>2</sub> ; hydroponics	Four weeks	TBARS content increased by 90 and 92%, respectively, in 25 µM and 125 µM As over control. ROS levels significantly enhanced in concentration dependent manner (OH <sup>•</sup> : 198 to 524%, H <sub>2</sub> O <sub>2</sub> : 234 to 539% from 10 to 100 µM, respectively).	[102]
<i>Glycine max</i> cv. JS 335	10 and 100 µM NaAsO <sub>2</sub> ; pre-soaked filter paper	2 and 5 days, respectively	LOX activity significantly enhanced with extended exposure (503 and 1193%, on 2 and 5 day).	[83]
<i>Arabidopsis thaliana</i>	100, 200 and 300 µM NaH <sub>2</sub> AsO <sub>4</sub> ; ½ MS medium	7 days	TBARS content increased by 16 and 38% in 200 and 300 µM As, respectively over control.	[103]
<i>Brassica napus</i> cv. Zheda 622 and ZS 758	200 µM NaAsO <sub>2</sub> ; peat and soil mixture	14 days	MDA content in roots enhanced by 101% in the cv. ZS 758 and by 178% in the cv. Zheda 622 over control. Superoxide radicals (O <sub>2</sub> <sup>•-</sup> ) and H <sub>2</sub> O <sub>2</sub> , approximately doubled over control in roots. Reactive oxygen species was increased in root and leaves only with 30 µg L <sup>-1</sup> over control while two-fold increase observed in roots and leaves of sensitive <i>N. sylvestris</i> .	[104]
<i>Nicotiana tabacum</i> cv. Wisconsin and <i>N. sylvestris</i>	10 and 30 µg L <sup>-1</sup> Na <sub>2</sub> HAsO <sub>4</sub> ·7H <sub>2</sub> O; perlite and sand (1:1); Hoagland solution	7 weeks	MDA content in sensitive <i>N. sylvestris</i> was increased with increasing As level, while there are no significant differences recorded in <i>N. tabacum</i> cv. Wisconsin.	[41]

## 6. Antioxidants and Arsenic Tolerance

The plant response to As and other abiotic stresses includes key ROS-scavenging enzymes such as: SOD, CAT, APX, MDHAR, DHAR, GR, GST, GPX, and POD [105,106]. The orchestration of antioxidant defense is performed by the balance of different enzymatic antioxidant, which involve removal of O<sub>2</sub><sup>•-</sup> (SOD), conversion of H<sub>2</sub>O<sub>2</sub> into water and molecular oxygen (CAT), scavenging of H<sub>2</sub>O<sub>2</sub> in the extra-cellular space (POD), conjugation of GSH to electrophilic compounds or hydrophobic compounds (GST), maintenance of ascorbate pool (MDHAR and DHAR), and scavenging of H<sub>2</sub>O<sub>2</sub> to water using ascorbate as specific electron donor (APX) [106].

Several proteomic investigations have observed the differential accumulation of antioxidant enzymes in plant tissues after As exposure (Table 2). Findings regarding this subject are important to gain information on As-induced antioxidant regulation at the translational level. However, more studies are needed on this subject in order to elucidate the relationship between antioxidant enzyme concentration and enzyme activity that is modulated by As exposure in plants. Further research is also needed in order to perform the qualitative evaluation involving isozyme profiling by gel-based approaches, which already performed by some authors that evaluated As-exposed plants [28,107]. Knowledge and achievements regarding As-induced oxidative stress tolerance might also be improved by using emerging proteomic approaches in the field of abiotic stress. For example, phosphoproteomics has been used to unravel plant tolerance mechanisms to heavy metals [108], even though there is a lack of information on this subject related to As toxicity.

**Table 2.** Some examples of proteomic studies involving the quantification of antioxidant enzymes in As-exposed plants.

Plant Species	Plant Organ	Proteomic Technology	Induced Enzymes	Reference
<i>Oryza sativa</i>	Root	In-gel, MALDI-TOF MS	GST	[109]
<i>Spinacia oleracea</i>	Leaf	2D-MS/MS	FeSOD, GST	[110]
<i>O. sativa</i>	Leaf	2-DE/MALDI-TOF-TOF	APX, GST, cytochrome c peroxidase	[111]
<i>O. sativa</i>	Leaf	2-DE/MALDI-TOF-TOF	Cu/ZnSOD	[112]
<i>Brassica napus</i>	Leaf	RPLC-MS-MS/iTRAQ	GR, Cu/ZnSOD, CAT, FeSOD	[104]
<i>B. napus</i>	Leaf	RPLC-MS-MS/iTRAQ	CAT, POD, SOD, GST	[113]
<i>Populus deltoides</i> and <i>Populus × euramericana</i>	Root	2-DE/MALDI-TOF-TOF-MS	Cu/ZnSOD, POD	[114]
<i>Artemisia annua</i>	Leaf	2-DE/MALDI-TOF-TOF-MS	APX, DHAR	[115]
<i>Zea mays</i>	Root	2-DE/MALDI-TOF-MS	GPX, Cu/ZnSOD	[116]

MALDI: Matrix-assisted laser desorption ionization; TOF: time-of-flight; MS: mass spectrometry; RPLC: High-pH reversed-phase liquid chromatography; iTRAR: Isobaric tag for relative and absolute quantitation; 2-DE: Two-dimensional gel electrophoresis. Abbreviations regarding antioxidant enzymes are explained in the text.

Despite the role that is played by enzymatic antioxidants, a more complete picture of the scavenging capacity in plants upon exposure to As can be achieved by the determination of non-enzymatic antioxidant molecules [41,117,118]. Components of the non-enzymatic antioxidant machinery include GSH, AsA, phenolic compounds (e.g., flavonoids), proline (Pro), cysteine, methionine, carotenoids,  $\alpha$ -tocopherol, polyamines, and sugars, as well as emerging components (e.g., anexins and dehydrins) [119]. Also noteworthy, metabolomic approaches have been contributed to in-depth understanding of As-related non-enzymatic antioxidants accumulation [43,120,121].

Many investigations have provided insights into mechanisms underlying antioxidant response of plants to As stress by evaluating changes in antioxidant enzyme activities and non-enzymatic antioxidant contents. Variations between results on this subject is explained to the effects of As, which are dose-, plant species- and experimental conditions-dependent [83,122–125]. For example, Bianucci et al. [126] observed that SOD, CAT, and GST augmented as well as overall decrease in GR and GPX activities and increased GSH contents under As exposure in a dose-dependent manner. These authors also identified the strong induction of GST activity as suitable biomarker of As toxicity in peanut plants. In another study, the activity of SOD, POX, and GR in *Lemna gibba* increased while concentration of As increased. In these plants, the anthocyanin content increased constantly, whereas CAT and APX activities as well as the content of chloroplastic pigments were reduced [127]. A higher POD activity in leaves, a reduced POD activity in roots, and induction of SOD and CAT activities in both leaves and roots were caused by As(V) addition in the growth medium of *V. faba* plants. In rice, the effects of As(III) treatment on the enhanced level of AsA and GSH as well as increased SOD, CAT, APX, chloroplast APX, GPOX, GR, and MDHAR activities were observed [128]. An investigation aimed at evaluating plants of *Azolla caroliniana* exposed to different concentrations of As found that, unlike the enzy-

matic molecules, some nonenzymatic antioxidants (e.g., anthocyanin) increased and were positively correlated with As concentration [129].

The existing and potential information derived from studies on As stress response confirms the importance of antioxidants towards helping plants to remove ROS. However, in several plant species, differences between antioxidant related As stress response parameters versus the ones related to As tolerance remain largely unknown. With regards to this focus, the comparative evaluation of As-tolerant and As-sensitive plants (or the comparison of plants with different degrees of tolerance/sensitivity, which includes As-hyperaccumulator plants and their sensitive counterparts) offer huge opportunities for deeper understanding of the contribution of antioxidants to As-induced oxidative stress tolerance. By evaluating two contrasting tobacco genotypes (As-sensitive *Nicotiana sylvestris* and As-tolerant *N. tabacum*, cv. 'Wisconsin'), some authors found meaningful differences in the carbohydrate status. Moreover, a higher total antioxidant capacity based on levels of antioxidant contents (e.g., AsA, GSH, and phenolic compounds) and activities was observed in the As-tolerant genotype [41]. In the study performed by Singh et al. [107], the castor tolerant genotypes presented increased SOD and GPX activities in roots, whereas castor sensitive genotypes showed decreases regarding these enzymes in a As concentration-dependent manner. CAT activity and Pro content were found to be increased in sensitive castor plants and unchanged in tolerant ones due to As(V) treatment [107]. The contents of Pro, GSH, AsA, activities of APX and CAT were used as parameters in observing the higher As sensitivity of *O. sativa* cv. Kshitish compared to cv. Nayanmani [130]. These investigations showed a complex variation in contents or activities according to different factors such as plant genotype, age, organ, as well as the time-length of plant exposure, and As concentration in the growing media. Noteworthy, a better antioxidant performance is not always explained by As-induced increases in non-enzymatic levels or enzyme activities of As-tolerant plants. Instead, there is a complex regulation involving the antioxidant related highest As tolerance degree, which depends on experimental conditions of investigations on this research field and peculiarly regarding the comparison relative to sensitive or less tolerant plants (Table 3).

**Table 3.** Examples of studies involving the evaluation of antioxidant molecules in contrasting plants for arsenic tolerance.

Plant Species	Plant Organs	Oxidative Stress Indicators *	Arsenic Levels	Contrasting Antioxidant Defense in As Tolerant Plants *		Reference
				Enzymes	Contents of Non-Enzymatic Antioxidants	
<i>Zea mays</i>	Leaf	Electrolytic leakage > MDA > H <sub>2</sub> O <sub>2</sub> >	NaAsO <sub>2</sub> (200 µM As), CdCl <sub>2</sub> (100 µM Cd); 45, 60, 75, and 90 d	SOD↑ POD↑ CAT↑ APX↑ GPX↑ GR↑	GSH↑ AsA↑	[131]
<i>Oryza sativa</i>	Root and shoot	MDA↑	As <sup>III</sup> (NaAsO <sub>2</sub> ; 10 and 25 µM) and As <sup>V</sup> (Na <sub>2</sub> HAsO <sub>4</sub> ; 0, 10, and 50 µM); 1, 4, and 7 d 50, 150, and 300 µM As(V); 24 and 96 h	APX↑ GPOX↑ SOD (root)↑	Overall stress responsive amino acid accumulation >	[132]
<i>O. sativa</i>	Leaf	MDA <	300 µM As(V); 24 and 96 h	APX > CAT > SOD >	Cysteine > Pro >	[133]
<i>Nicotiana sylvestris</i> and <i>N. tabacum</i>	Leaf and root	MDA = ROS <	Na <sub>2</sub> HAsO <sub>4</sub> ·7H <sub>2</sub> O (10 and 30 µg L <sup>-1</sup> ); 7 weeks	APX (leaf)↓ GST (leaf)↓ POD(leaf)↓ APX (root)↑ GST (root) = CAT (root)↓ CAT (leaf)↑	AsA (root)↑ Anthocyanin (leaf) = GSH/GSSG↓ Carotenoids, Phenolic compounds (leaf) = Phenolic compounds (root)↑ Pro (leaf)↑ Total glutathione (root) > Carbohydrate status =	[41]

Table 3. Cont.

Plant Species	Plant Organs	Oxidative Stress Indicators *	Arsenic Levels	Contrasting Antioxidant Defense in As Tolerant Plants *		Reference
				Enzymes	Contents of Non-Enzymatic Antioxidants	
<i>O. sativa</i>	Root and shoot	MDA <sup>LI</sup> H <sub>2</sub> O <sub>2</sub> <sup>LI</sup>	Na <sub>2</sub> HAsO <sub>4</sub> ·7H <sub>2</sub> O; 18 d	SOD↑ CAT <sup>LD</sup>	Pro↑	[134]
<i>O. sativa</i>	Root and shoot	MDA <sup>LI</sup> H <sub>2</sub> O <sub>2</sub> <sup>LI</sup>	25, 50 and 75 μM Na <sub>2</sub> HAsO <sub>4</sub> ·7H <sub>2</sub> O; 18 d	SOD <sup>LI</sup> CAT <sup>LD</sup>	Pro <	[135]
<i>Z. mays</i>	Leaf	MDA < H <sub>2</sub> O <sub>2</sub> <	2.5, 7.5, and 12.5 μg mL <sup>-1</sup> NaHAsO <sub>4</sub> ·7H <sub>2</sub> O in 30% HNS; 3 and 7 d	SOD > GR > APX < GPOX < CAT <	Carotenoids↑ GSH =	[136]
<i>O. sativa</i>	Leaf	TBARS < H <sub>2</sub> O <sub>2</sub> <	4 μg mL <sup>-1</sup> As(III) (NaHAsO <sub>4</sub> ·7H <sub>2</sub> O) and As(V) (NaAsO <sub>2</sub> ); 14 d	SOD < APX > GR > GST >	GSH <	[137]
<i>O. sativa</i>	Root and shoot	H <sub>2</sub> O <sub>2</sub> <sup>LI</sup>	25 μM, 50 μM, and 100 μM Na <sub>2</sub> HAsO <sub>4</sub> ·7H <sub>2</sub> O; 18 d	CAT <sup>LD</sup> APX <sup>LI</sup> GR <sup>LI</sup> GST↑	AsA <sup>LI</sup> GSH <sup>LI</sup> Pro <sup>LI</sup>	[130]
<i>Pteris vittata</i> and <i>P. ensiformis</i>	Fronde	TBARS < H <sub>2</sub> O <sub>2</sub> <	133 and 267 μM of As as Na <sub>2</sub> HAsO <sub>4</sub> ·7 H <sub>2</sub> O; 1, 5 and 10 d	NC	AsA > Carotenoid > GSH >	[13]
<i>Ricinus communis</i>	Leaf	MDA = H <sub>2</sub> O <sub>2</sub> =	100 and 200 μM Na <sub>2</sub> HAsO <sub>4</sub> ·7H <sub>2</sub> O; 21 d	Mn-SOD =	Carotenoid (no contrasting differences)	[45]
<i>R. communis</i>	Leaf and root	NC	100 and 200 μM As(V)	CAT = SOD↑ GPOX↑	Pro =	[107]
<i>Brassica juncea</i>	Shoot	NC	As(V) (50 μM and 500 μM) and As(III) (25 μM and 250 μM); 7 d and 15 d	NC	Cysteine↑ GSH↑ Non-protein thiols↑	[138]
<i>B. juncea</i>	Shoot	MDA =	As(V) (50 and 500 μM) and As(III) (25 and 250 μM); 7 or 15 d	DHAR↑ MDHAR↑ SOD > APX↑ GPOX↑	GSH↑ GSH/GSSG↑ Pro↑	[139]
<i>O. sativa</i>	Root and shoot	NO < NADPH oxidase < Ascorbate oxidase <	As(V) (NaAsO <sub>2</sub> ; 5, 10, 25 μM); 15 d	GPX >	AsA > Carotenoids <sup>LD</sup> Pro >	[140]
<i>P. cretica</i> and <i>Spinacia oleracea</i>	Shoot	NC	20 and 100 mg As kg <sup>-1</sup> soil; NC	NC	Carotenoids <sup>LD</sup>	[42]

GPX: glutathione peroxidase; GPOX: guaiacol peroxidase; NC: not cited in the original article. Abbreviations regarding other antioxidant molecules are explained in the text. GSH:GSSG: ratio between reduced and oxidized glutathione. MDA: Malondialdehyde; NO: Nitric oxide; TBARS: Thiobarbituric acid reactive substances; \*↑: contrasting As-induced increases observed in plants with the higher tolerance degree in relation to the As-induced response observed in the sensitive (or less tolerant) counterparts; LI: Lower As-induced increases observed in plants with the higher tolerance degree compared to their sensitive (or less tolerant) counterparts; LD: Lower As-induced decreases observed in plants with the higher tolerance degree compared to their sensitive (or less tolerant) counterparts; ↓: As-induced decreases observed in tolerant plants, whereas sensitive (or less tolerant) counterparts presented increases or unchanged values; = unchanged value observed in tolerant plants after As exposure, whereas sensitive (or less tolerant) counterparts presented increases in contents of oxidative stress indicators or changes in levels (non-enzyme) or activities (enzyme) of antioxidants; > (higher) or < (lower) value observed in tolerant plants compared to their sensitive (or less tolerant) counterparts under the As exposure condition.

## 7. Approaches in Enhancing Oxidative Stress Tolerance in Plants Exposed to Arsenic

Thirst of plants researchers are increasing for searching and establishing proper strategies to increase plant defense mechanisms upon As-induced oxidative stress. Therefore, exogenous different elicitors like plant nutrients, hormone, antioxidants, osmolytes, signaling molecules, different chelating agents, microbial inoculants, organic amendments etc. were used in different plant species upon exposure to As stress to evaluate their roles in reducing oxidative injury through upregulating antioxidants activities (Table 4).

**Table 4.** Exogenous elicitors-mediated oxidative stress tolerance in plant under arsenic toxicity.

Plant Species	Arsenic Levels	Exogenous Elicitors	Defense Responses	References
<i>Oryza sativa</i> L. cv. minakshi	60 $\mu\text{M}$ $\text{Na}_2\text{AsO}_3$ ; 7d	10 $\mu\text{M}$ Se ( $\text{Na}_2\text{SeO}_4$ ); co-treatment	Reduced the generation of $\text{H}_2\text{O}_2$ and MDA by 23 and 35%, respectively. Decreased AsA content by about 15%. Reduced the activity of CAT, SOD and APX by 8, 23 and 9%, respectively. Suppressed ROS generation as $\text{O}_2^{\bullet-}$ and $\text{H}_2\text{O}_2$ contents and their histochemical detection.	[141]
<i>Vicia faba</i> L. cv. Tara	5 $\mu\text{M}$ $\text{Na}_2\text{AsO}_3$ , 27 d	30 mM $\text{CaCl}_2$ , as co-treatment	Reduced NADPH oxidase and glycolate oxidase (GOX) activities. Increased SOD, APX, MDHAR and DHAR activities.	[73]
<i>O. sativa</i> L. var. Narendra	50 $\mu\text{M}$ $\text{NaAsO}_2$ , 15 d	Si, silicon (10 $\mu\text{M}$ ); co-treatment	Strengthen membrane stability. Increased AsA content and AsA/DHA with higher activity of MDHAR, DHAR	[142]
<i>Arabidopsis thaliana</i> L.	100 and 200 $\mu\text{M}$ $\text{Na}_2\text{HAsO}_4 \cdot 7\text{H}_2\text{O}$ , 24 h	1 $\mu\text{M}$ 24-Epibrassinolide (EBL)	Increased total antioxidant capacity with higher SOD and CAT activities. Reduced MDA content.	[143]
<i>O. sativa</i> L. cv. Swarna Sub1	50 $\mu\text{M}$ $\text{NaAsO}_2$ , 240 h	10 $\mu\text{M}$ of ABA, 24 h as pretreatment	Reduced $\text{O}_2^{\bullet-}$ and $\text{H}_2\text{O}_2$ by 50 and 38%, respectively. Reduced lipid peroxidation (TBARS) by 48%. Reduced membrane damage as decreased EL.	[125]
<i>Zea mays</i> L. cv. "DK5783"	0.1 mM $\text{Na}_2\text{HAs}_4\text{O}_7 \cdot 7\text{H}_2\text{O}$ , 28 d	0.5 mM salicylic acid (SA as 2-hydroxybenzoic acid), pretreatment, 7 d.	Significantly increased GSH/GSSG with higher GR activity. Upregulated antioxidants activity like SOD, CAT, APX and GPX. Reduced $\text{H}_2\text{O}_2$ , MDA production and EL.	[144]
<i>O. sativa</i> cv. Sarjoo52	25 $\mu\text{M}$ $\text{NaAsO}_2$ , 7 d	Sodium nitroprusside (SNP) (30 $\mu\text{M}$ ; NO donor	Decreased SOD activity with higher activity of CAT and POD. Improved AsA/DHA and GSH/GSSG by improving AsA and GSH content with reduction of DHA and GSSG level. Elevated the activity of enzymatic components of AsA-GSH pathway like APX, GR, MDHAR and DHAR. Decreased the production of $\text{H}_2\text{O}_2$ and TBARS.	[145]
<i>Lemna valdiviana</i>	4.0 mg $\text{L}^{-1}$ $\text{Na}_2\text{HAsO}_4 \cdot 7\text{H}_2\text{O}$ , 24 h	100 $\mu\text{M}$ JA, co-treatment	Reduced $\text{O}_2^{\bullet-}$ generation detected by histochemical staining. Lowered SOD, CAT, GPX, APX activities. Improved GR activity.	[74]

Table 4. Cont.

Plant Species	Arsenic Levels	Exogenous Elicitors	Defense Responses	References
<i>Brassica napus</i> L. cvs. Zheda 622 and ZS 758	200 $\mu\text{M}$ $\text{NaAsO}_2$ , 14 d	1.0 $\mu\text{M}$ MeJA	Decreased MDA content with the higher activity of SOD, POD, CAT, APX. Elevated the GSH and GSSG level with the increasing GR activity. Increased AsA content. Suppressed $\text{H}_2\text{O}_2$ , MDA and EL by 63, 57, and 44%, respectively. Increased the activity of SOD, CAT, APX, MDHAR, DHAR, GR and GST by 32, 71, 15, 43, 71, 19, and 27%, respectively.	[146]
<i>Pisum sativum</i> L.	20 $\mu\text{M}$ $\text{NaAsO}_2$ , 31 d	200 $\mu\text{M}$ $\text{H}_2\text{S}$ (NaHS), co-treatment	Augmented the content of AsA, GSH and GSSG by 67, 25 and 61%, respectively. Reduced the generation of MG by 35% with 18 and 44% higher activity of Gly I, and Gly II, respectively. Lowered cysteine content in both shoot and root (by 7 and 18%).	[99]
<i>O. sativa</i> L. var. Pusa Basmati	150 $\mu\text{M}$ $\text{NaAsO}_2$ ; 48 h	100 $\mu\text{M}$ NO SNP; 24 h as pretreatment	Reduced $\text{H}_2\text{O}_2$ and MDA content by 7 and 19%, respectively in shoot and by 7 and 16% in roots. Decreased the activity of CAT, SOD, APX and GR in both shoot and root. Reduced $\text{H}_2\text{O}_2$ and MDA in leaves (13 and 28%, respectively) and roots (18 and 20%, respectively).	[147]
<i>B. juncea</i> var. Pusa Jagannath	150 $\mu\text{M}$ $\text{NaAsO}_2$ , 48 h $\text{NaAsO}_2$	100 $\mu\text{M}$ SNP, pre-incubation started before 24 h of stress	Decreased cysteine and Pro content significantly. Lowered down the level of GSH with reduction in the activities of SOD, CAT, APX and GR. Reduced the thiol components including both total thiol and non-protein thiol. Reduced MDA and $\text{H}_2\text{O}_2$ content.	[148]
<i>Solanum lycopersicum</i> L. cv. Pusa ruby	10 $\mu\text{M}$ $\text{Na}_2\text{HAsO}_4$ , 7 d	250 $\mu\text{M}$ citric acid (CA)	Elevated the non-enzymatic antioxidants content with higher (62%) CAT activity. Decrease the activity of APX and GR (89%). Reduced oxidative stress by lowering MDA and $\text{H}_2\text{O}_2$ contents.	[149]
<i>S. lycopersicum</i> L. cv. Pusa ruby	10 $\mu\text{M}$ $\text{Na}_2\text{HAsO}_4$ , 7 d	250 $\mu\text{M}$ GSH	Elevated the CAT activity by 96% with lower down of APX and GR (123%) activities.	[149]
<i>Hydrilla verticillata</i>	3 $\text{mg L}^{-1}$ as $\text{As}_2\text{O}_3$ and $\text{Na}_2\text{HAsO}_4 \cdot 7\text{H}_2\text{O}$ ; 10 d	200–2000 $\mu\text{g L}^{-1}$ oxalic acid (OA)	Decreased TBRAS content with higher activity of SOD, POD and CAT	[150]

Table 4. Cont.

Plant Species	Arsenic Levels	Exogenous Elicitors	Defense Responses	References
<i>O. sativa</i> L.	150 $\mu\text{M}$ $\text{Na}_3\text{AsO}$ , 2 d	20 $\mu\text{M}$ melatonin, co-treatment	<p>Reduced protease activity. Lowered MDA content by 30% and LOX activity by 21%. Reduced MG content (14%) with higher activity of Gly I and Gly II by 20 and 12%, respectively. Decreased NADP oxidase (NOX) activity by 31%. The activity of ascorbic acid oxidase (AAO) and nitrate reductase (NR) were reduced and increased, respectively. Increased anthocyanin, flavonoid, xanthophylls, and total phenolic content by 92, 40, 90, and 20%. Increased total antioxidant capacity with 48% higher AsA content. Increased phenylalanine ammonia lyase (PAL) activity by 29%. Reduced ROS including <math>\text{O}_2^{\bullet-}</math> and <math>\text{H}_2\text{O}_2</math> contents and the NADPH oxidase and GOX activity.</p>	[151]
<i>V. faba</i> L. cv. Tara	5 $\mu\text{M}$ $\text{Na}_2\text{AsO}$ , 27 d	50 $\mu\text{M}$ melatonin as co-treatment	<p>Decreased membrane damage as indicated by lower MDA content and EL. Strengthened antioxidants defense mechanism by increasing SOD, AsA-GSH pathways.</p>	[73]
<i>Vigna radiata</i>	23 $\text{mg kg}^{-1}$ $\text{Na}_2\text{HAsO}_4 \cdot 7\text{H}_2\text{O}$ , 7 d	<i>Acinetobacter lwoffii</i> RJB-2	Reduced MDA content and EL.	[152]
<i>Camellia sinensis</i> L.	25 $\mu\text{M}$ $\text{Na}_2\text{HAsO}_4 \cdot 7\text{H}_2\text{O}$ , 30 d	100 $\mu\text{M}$ melatonin for 24 h as pretreatment	<p>Reduced <math>\text{O}_2^{\bullet-}</math> and <math>\text{H}_2\text{O}_2</math> with lower MDA level. Elevated APX, SOD, CAT and POD activities with higher total antioxidants capacity. Reduced NOX activity by 39%. Decreased TBARS by 47%. Reduced <math>\text{O}_2^{\bullet-}</math> and <math>\text{H}_2\text{O}_2</math> production by 54 and 48%, respectively led to lower 37% of EL.</p>	[153]
<i>Salvinia natans</i> L.	500 $\mu\text{M}$ $\text{NaAsO}_2$ , 7 d	500 $\mu\text{M}$ of 2,4-dichlorophenoxyacetic acid (2,4-D), 3 d as pretreatment	<p>Elevated SOD and APX activity with reduction of CAT and GPX. Increased AsA content and GSH/GSSG with the elevated response of enzymatic components like MDHAR, DHAR and GR activity.</p>	[154]
<i>Glycine max</i> var. JS 20–29	500 $\mu\text{M}$ $\text{Na}_2\text{HAsO}_4 \cdot 7\text{H}_2\text{O}$ , 7 d	1 $\mu\text{M}$ $\text{H}_2\text{O}_2$ , 24 h as pretreatment	<p>Reduced <math>\text{O}_2^{\bullet-}</math>, <math>\text{H}_2\text{O}_2</math> and MDA content. Elevated the activity of APX, MDHAR, DHAR and GR. Increased AsA, DHA, GSH, and GSSG contents resulted higher AsA/DHA and GSH/GSSG status.</p>	[155]

### 7.1. Use of Plant Nutrients

Different plant nutrient receiving attention for their ability to mitigate the oxidative stress and damage upon As exposure [156,157]. Calcium (Ca)-induced lower oxidative stress was reported by Rahman et al. [156] in *O. sativa* upon As stress, while without

stress condition, Ca did not showed any changes in  $H_2O_2$  and MDA levels. Calcium supplementation increased antioxidants activities including SOD, CAT, GPX, GST in As-stressed rice which contributed in reduction of  $H_2O_2$  [156]. Calcium also causes the stimulation of AsA-GSH pool in plants upon As toxicity which has strong relationship in regulation of  $H_2O_2$  detoxification and thus enhances oxidative stress tolerance with lower MDA level. For instance, higher APX, MDHAR, DHAR activities with lower GR activity caused increment of AsA/DHA and GSH/GSSG redox balance along with lower oxidative stress in As-treated rice with Ca [156]. Exogenous application of Ca and sulfur (S) significantly modulating ROS detoxification in As-stressed plant through strengthening the antioxidants responses [157]. Lower  $H_2O_2$  accumulation by S and Ca in separate and as well as combined application resulted in reduction of MDA in As-stressed *Brassica* plants where Ca caused comparatively better results [157]. In addition, Ca and S-treated *Brassica* showed higher AsA/DHA and GSH/GSSG redox in both root and leaves tissue which were because of Ca and S-mediated elevated APX, DHAR and GR activities and thus resulted in lower ROS [157]. Arsenic-induced oxidative stress was mediated by Ca supplementation which caused higher tolerance in *V. faba* by suppressing both ROS generation and respective enzymatic activity resulted in lower EL and MDA level [73]. This Ca-induced higher As-tolerance was stronger in combination with melatonin where highest reduction of oxidative damage was measured along with elevated activity of antioxidant system including SOD, APX, GR, MDHAR, DHAR and GST activities.

### 7.2. Use of Phytohormones

Phytohormones are very potential to improve the plant antioxidant defense mechanism consisting of both enzymatic and non-enzymatic stuffs for suppressing metal-induced oxidative damage [158]. Methyl jasmonate (MeJA), for example, is effective to reduce oxidative stress as revealed by lowered ROS generation, elevated redox state of AsA and GSH, strengthened enzymatic antioxidants activities and better membrane stability in plants upon As toxicity [159,160]. Exogenously 1  $\mu$ M MeJA caused the significant reduction of  $H_2O_2$  and  $OH^\bullet$  about 20 and 17%, respectively led to decrease in lipid peroxidation (as MDA; about 27%) in 200  $\mu$ M As-exposed *B. napus* [159]. This MeJA-induced oxidative stress tolerance in As-stressed *B. napus* was acquired due to increasing plant antioxidant defense mechanism through elevated AsA and GSH content along with higher activities of enzymatic components like SOD, POD, CAT, APX and GR. Likely, As-stressed rice showed lower membrane damage revealed by reduced MDA and EL with the application of MeJA led to decrease activities of SOD, POD, CAT and APX [160]. Such MeJA-induced lower membrane damage in As-stressed plants describe the lower generation of ROS which also correlated with the lesser activity of enzymatic antioxidants. Ascorbate-glutathione cycle is one of the vital mechanisms for regulating  $H_2O_2$  metabolism in plant cell and thus keep its level beyond toxic, which is also strengthened by phytohormones supplementation under As stress [125,144]. The higher AsA-GSH redox status by plant hormones thus contributed in reduction of ROS and consequent oxidative damage like membrane injury, for instance, salicylic acid (SA)-mediated lower  $H_2O_2$ , MDA production and EL in As-stressed *Z. mays* [144]. Methyl jasmonate diminished oxidative stress through increasing the activity of antioxidant enzymes and decreasing As accumulation by modulating arsenic transporters of rice plants. Addition of MeJA in rice plants under As stress improved the level of AsA, AsA/DHA, GSH and GSH/GSSG, increased the activity SOD, APX and POD. The oxidative stress ( $H_2O_2$  and MDA) was decreased in those MeJA treated rice plants. The augmented tolerance of those rice plants was also observed in terms of increased Chl content, Chl fluorescence and biomass production, yield components and yield [161].

Similarly, other phytohormones are also significant in reducing As-induced oxidative stress through strengthening antioxidant defense mechanism. For instance, exogenous application of jasmonic acid alleviated the As-induced oxidative stress by 36% of reducing ROS with elevated activity of SOD, CAT, APX and GR in *L. valdiviana* [74], while cytokinin (e.g., kinetin)-induced lower down of ROS in As-stressed *P. cretica* [162]. The abscisic acid

(10  $\mu\text{M}$ ) was used in *O. sativa* as pretreatment for 24 h to strengthen As tolerance and this pretreatment caused the upto 50 and 38% reduction of  $\text{O}_2^{\bullet-}$  and  $\text{H}_2\text{O}_2$ , respectively which resulted in 48% lower down of lipid oxidation with improvement of membrane stability [125]. This ABA-mediated relief of oxidative damage in As-stressed plant through ABA-induced elevated response of AsA-GSH pathway. Such As-mediated oxidative stress was downregulated by the exogenous SA in *Z. mays* [144]. Therefore, exogenous plant hormones are potential candidates for regulating As-induced oxidative stress for increasing plant tolerance through strengthening the plant antioxidant defense mechanism including both non-enzymatic and enzymatic components (Table 4).

### 7.3. Use of Signaling Molecules

Supplementation of signaling molecules like nitric oxide (NO), hydrogen sulfide ( $\text{H}_2\text{S}$ ) and  $\text{H}_2\text{O}_2$  causes the stimulation in the antioxidants system, leads to reduction of oxidative stress in plants. We summarize the involvement of the signaling behavior of these in suppressing the As-mediated oxidative stress (Table 4).

Exposure of As-induced higher ROS and structural injury of cellular integrity including lipid peroxidation and membrane injury were significantly improved in all NO,  $\text{H}_2\text{S}$  and  $\text{H}_2\text{O}_2$ -treated plants [99,157,163]. The accumulation of ROS was reduced in signaling molecules treated As-stressed plant, for instance, both NO and  $\text{H}_2\text{S}$  reduced  $\text{O}_2^{\bullet-}$  and  $\text{H}_2\text{O}_2$ ,  $\text{OH}^\bullet$  accumulation while exogenous application of lower concentration of  $\text{H}_2\text{O}_2$  has the capability to suppress  $\text{O}_2^{\bullet-}$  and  $\text{H}_2\text{O}_2$  later resulted in better cellular function as well as lowered the oxidative damage as caused lower lipid and protein oxidation. Consequently, regulation of As-induced ROS metabolism requires the intensive involvement of antioxidants activities. Other studies reported about the participation of NO,  $\text{H}_2\text{S}$  and  $\text{H}_2\text{O}_2$  as external approaches to empower both enzymatic and non-enzymatic antioxidants directly or indirectly to mitigate As-induced oxidative stress [99,145,147].

Exogenous sodium nitroprusside (SNP; as NO donor) in presence of As caused the reduction of enzymatic antioxidants activity like SOD, CAT and POD which in accordance with NO-induced lowered level of  $\text{O}_2^{\bullet-}$ ,  $\text{H}_2\text{O}_2$ , EL by 1.4-, 1.5- and 1.5-fold with lower MDA in *Spirodela intermedia* [164]. Transcriptional expression of the PCS, GSH1, MT2, and ABC1 were improved by NO supplementation in As stressed tomato plants which increased sequestration of As in root and decreased further translocation of As to the shoot. Exogenous NO also modulated proline metabolism and caused higher accumulation of GSH. The resulted oxidative stress relaxation was evident from  $\text{H}_2\text{O}_2$  reduction and protection of photosynthetic apparatus [165]. In another study, the function of nitrate reductase (NR)-synthesized nitric oxide (NO) in the MeJA-induced tolerance of arsenic (As) stress was studied in rice. The positive effects were clear from the increased expression of GSH1, PCS, and ABCC1 genes, higher GSH and PCs contents in the roots and leaves, and increased activity of SOD, CAT, APX and GR. The ultimate oxidative stress reduction is apparent from decreased  $\text{H}_2\text{O}_2$ , MDA and EL [166]. As an emerging signaling molecule,  $\text{H}_2\text{S}$  regulates the key antioxidants activities for keeping lower-level ROS and subsequent better integrity of cellular components. In *P. sativum*, non-enzymatic antioxidants AsA and GSH contents were elevated with the supplementation of  $\text{H}_2\text{S}$  in exposure to As through the higher activity of responsible enzymes like APX, MDHAR, DHAR and GR [99]. Therefore, both of AsA and GSH were actively worked on scavenging As-induced higher  $\text{H}_2\text{O}_2$  level through the regulation of the redox status of AsA and GSH. Not only that, exogenous  $\text{H}_2\text{S}$  also raised the activity of SOD, and CAT which are also acted on  $\text{O}_2^{\bullet-}$  converting into  $\text{H}_2\text{O}_2$  for further action by AsA-GSH cycle. In this study, higher GST activity and GSH also described the roles of GSH in detoxification of lipid and protein peroxidation products used as substrate and thus recovered plant from oxidative status. Although  $\text{H}_2\text{O}_2$  is harmful at extreme level but under threshold level it also acts as signaling molecules to regulate plant stress tolerance. Regarding this, it was reported that exogenous  $\text{H}_2\text{O}_2$  (1  $\mu\text{M}$ ) regulated the ROS metabolism to keep them under beneficial level through the activation of APX, MDHAR, DHAR, and GR in stressed plants due to its signaling roles [157]. However, the

actual mechanism of signaling molecules-mediated plants recovery upon As stress is still lacking which demand further extensive studies.

#### 7.4. Use of Chelating Agents

Chelating agents mediated higher upregulation of plant antioxidant defense system for getting relief from As-induced oxidative stress is still not explored widely. Therefore, this approach for getting As-tolerance behavior in cultivated crop species could be vital as these also have metal elimination properties. Citric acid (CA) is known as harmless compound which is able to increase the plant antioxidants capability and thus reduced As-induced oxidative damage through declining the ROS accumulation and lipid peroxidation [167]. Citric acid mediated mitigation of oxidative stress and the plant tolerance in As exposure was due to the upregulation of antioxidant enzymes like SOD, CAT, and [149]. However, the role of chelating compound is very species-dependent along with their dose level. Effect of ethylenediaminetetraacetic acid (EDTA) was studied in regulation of As-induced oxidative stress by declining ROS and lipid peroxidation [168,169]. Application of EDTA enhanced As-induced H<sub>2</sub>O<sub>2</sub> production, but reduced lipid peroxidation [169].

#### 7.5. Use of Soil Amendments

Soil amendments are an eco-friendly and cost-effective approach for betterment of soil health to achieve food safety in this era of climate change. Therefore, researchers have been tried biochar to amend As toxicity and thus improve plant tolerance. Toxic level of As treated higher oxidative stress markers like membrane damage, H<sub>2</sub>O<sub>2</sub> and MDA in *G. max* were declined when biochar (made from waste wood chips) was applied [170]. Due to the addition of biochar antioxidants defense mechanisms were upregulated in As-treated plants, for instance, SOD, CAT, APX, GPX, GR and GST oxidative injury was prohibited significantly resulted in protection of *G. max* for oxidative stress [170].

Peanut and canola straw biochar was used to evaluate its potentiality as an organic amendment to improve plant tolerance and growth upon As toxicity [171]. This greenhouse-based study showed the protective effects of biochar on suppressing As-induced oxidative stress (indicated by lowering MDA, H<sub>2</sub>O<sub>2</sub> and O<sub>2</sub><sup>•-</sup> about 82, 49, and 45%, respectively) in soybean which gave the indication of biochar mediated stronger antioxidants defense mechanism in stressed plant and forecast its future useability. Kamran et al. [171] also disclosed about the comparative better performance of peanut straw biochar than canola based.

#### 7.6. Use of Beneficial Microbes

Microbial inoculants effectively regulate the plant antioxidants defense capacity upon As-induced oxidative stress and thus enhance plant tolerance [172]. In addition, this protective effects of microbes in stimulating plant antioxidants mechanism depends on microbes' species, strains which can be said as strain-specific or specifically antioxidants-specific, As toxicity levels and plants species [173]. Bacterial influence for plant has been documented as beneficial in some extent. Previously, some researchers reported about plant growth-promoting rhizobacteria (PGPR) significantly regulated plant antioxidants enzymes activity. About 100 mg kg<sup>-1</sup> of both As(III) and As(V) treatments-induced higher enzymatic antioxidants responses were reduced significantly in *V. radiata* [174]. Incubation of As-stressed *V. radiata* with *Exiguobacterium* showed lower activity of SOD, CAT, APX and GPX near to control treatment thus resulted bacteria-mediated suppression of oxidative stress (as lessening ROS generation. Likely, several PGPR documented for increasing antioxidants activity like SOD by *Bacillus cereus* [175], SOD and CAT by *Populus deltoides* [176], APX and CAT by *B. licheniformis* [177], SOD and CAT (about 27 and 62%, respectively) by *B. aryabhatai* [178] in As-stressed plant. Consequently, in recent study of Xiao et al. [172] was about modulation of antioxidants defense system in As-stressed rice by different PGPR for attuning lower ROS production. *Pseudomonas mosselii*, *B. thuringiensis*, and *Bacillus* sp. JBS-28 inoculation showed the reduction of As-mediated oxidative damage through promoting the antioxidants capacity like SOD and POX activity which directly

scavenge the ROS. Thereafter, in case of wheat, *Brevundimonas intermedia* and *P. gessardii* modulated higher SOD and APX activities were revealed by the higher expression of their respective gene at As exposure [179]. Ghosh et al. [180] reported about *Pantoea dispersa*—modulated higher SOD and CAT activities with less MDA and thus As-tolerant bacterial strains were recommended for using in improving membrane stability of *O. sativa* upon As toxicity. However, the innate mechanisms in antioxidant defense modulation in As-stressed plants by PGPR are still unknown and which demand further extensive studies. *Piriformospora indica* improved the root sequestration of As, decreased As translocation and improved the AsA-GSH homeostasis which altogether contributed better photosynthetic performance and reduced the oxidative stress. *P. indica* sequestered As in the roots through upregulating the expression of PCS1 and PCS2 genes. It also reduced As accumulation in shoot by downregulating the expression of Lsi2, Lsi6, Nramp1 and Nramp5. Modulating AsA-GSH homeostasis *P. indica* decreased the MDA level of rice plant [181].

### 7.7. Other Chemical Elicitors

Plant researchers are also interested to explore the new, most adaptive and efficient technology for increasing plant tolerance against As stress. Therefore, antioxidants, osmolytes, polyamine and other chemical elicitors likely have been used in small scale previously and still now need more exploration to understand and develop these exogenous protectant-mediated mechanisms involved in plant oxidative stress tolerance. Notable, melatonin has gained the attention of plant researchers' community due to its antioxidant's potentiality specially its mitigating nature against the oxidative stress-mediated cellular damage [182]. Exogenous melatonin caused the stimulation in defense system of rosemary seedlings upon As stress as it improved cell membrane integrity with reduction of oxidative damage through increment of enzymatic antioxidants capacity [183]. Samanta et al. [184] reported that melatonin treatment improved As-induced oxidative stress tolerance by triggering the antioxidative machinery where increased the total antioxidants activity with elevated non-enzymatic antioxidants content like AsA, phenolic compound resulted in the reduction of oxidative damage. Similarly, melatonin-mediated reduction of ROS with upregulation of antioxidants activity like APX, SOD, CAT, POD was reported in As-stressed *Camellia sinensis* [153].

As stress management approach, use of non-enzymatic antioxidants is also efficient for suppressing oxidative stress by improving plant antioxidant capacity of plant upon As-toxicity. Exogenous AsA (250 and 500 mg kg<sup>-1</sup>) showed the amelioration of 15 µM As-induced oxidative stress through enhancing the capacity of AsA-GSH cycle in rice maintaining the sufficient level of both AsA and GSH [185]. Ascorbate-treated plant showed the reduction of ROS and MDA contents as indication of lowered oxidative damage with higher AsA/DHA and GSH/GSSG ratios. Jung et al. [186] studied the role of exogenous GSH (50 and 100 mg kg<sup>-1</sup>) on biochemical responses of ROS and antioxidant levels in 14 d-old *O. sativa* seedlings at As (15 µM) exposure. This GSH treatment reversed the As-induced oxidative damage with the improvement of antioxidants activity. Hydroponically grown rice seedling with the foliar application of GSH declined As-induced oxidative stress indicated by lower ROS (O<sub>2</sub><sup>•-</sup> and H<sub>2</sub>O<sub>2</sub>) and lipid peroxidation (MDA content), whereas increased the redox balance of AsA/DHA and GSH/GSSG with higher activity of MDHAR, DHAR and GR. Therefore, it can be suggested from both of above-mentioned studies that exogenous AsA and GSH causes the higher induction of AsA-GSH cycle, which re-established the cellular redox status.

The osmolyte Pro also regulates antioxidants capacity in stressed plant besides of its role on maintaining osmotic status. As a vital amino acid, Pro helps in scavenging stress-mediated higher ROS and protects plants from oxidative damage and thus stabilizes cellular structure including membrane [163]. In the experiment [163], Pro (25 µM) was applied in As-treated (25 µM) *Solanum melongena* and Pro fed plants showed the decline of O<sub>2</sub><sup>•-</sup>, H<sub>2</sub>O<sub>2</sub> and MDA level which were elevated in stress treatment alone which were because of the stimulation in activities of SOD, CAT and POD.

Phenolic compounds like chlorogenic acid and hesperidin are also well recognized as non-enzymatic antioxidants those are strongly able to neutralize the harmful free radicals besides of their metal chelating actions. Both chlorogenic (100  $\mu\text{M}$ ) and hesperidin (50  $\mu\text{M}$ ) were selected for using them singly or combined on maize plants upon As-stress (100  $\mu\text{M}$ ) [98]. This treatment altered the stress-induced reduction of antioxidants mechanism in maize by elevated the actions of SOD, CAT, POD, GST, GPX, MDHAR and GR which resulted in suppressing of ROS and TBARS content with maintaining higher redox status of AsA/DHA and GSH/GSSG. Thus, phenolic compounds are able to contributing in maintaining the cellular redox balance through the regulating the AsA-GSH cycle along with other potential antioxidants enzymes activities [98].

In recent years, nanoparticles (NPs), which are ultrafine particles presenting at least one dimension in <100 nm range, have gained much attention in topics related to modern agricultural research [187]. This novel and emerging nanotechnology approach has been reported to improve the production of some plant species by enhancing tolerance to environmental stresses [187,188] and promote beneficial changes regarding antioxidants. This includes increased enzyme activities and non-enzymatic contents in As-exposed plants of several species such as rice [189–191], soybean [192], maize [193], tomato [194] and mung bean [195]. Thus, besides covering the field of environmental protection and As toxicity alleviation in plants [196,197], the potential application of NPs highlights the role of antioxidant enzymes and non-enzymatic antioxidant molecules as important molecules for the modulation of tolerance to As-induced oxidative stress. Zinc nanoparticles (ZNO NPs) positively affect As-induced oxidative stress in rice by stimulating enzymatic antioxidants activity including SOD and CAT which lead to about 13–30% reduction of MDA content [198]. Similarly, ZNO NPs mediated further higher SOD activity was also measured in As-stressed (2 mg L<sup>-1</sup>) rice where 10 and 100 mg L<sup>-1</sup> concentration of ZnO NP showed better results [190].

## 8. Genetic Engineering in Enhancing Antioxidant Defense towards Arsenic Tolerance

Under increasing As concentrations, plants suffer a redox imbalance resulting in an increase in ROS levels which induces damages on the cellular biomolecules and functions [199]. Beside to the current techniques used for reduction of As in soil and water remediation, transgenic approaches have to be strengthened to solve this problem [200]. These approaches can be addressed considering different criteria such as working with genes responsible for As absorption, movement and sequestration in vacuoles, and enzymes and proteins regulating As conversion and GSH and PC metabolism [201].

Regarding As transporters, they can be classified as plasma membrane or vacuole transporters. The main plasma membrane transporters are aquaglyceroporins and phosphate transporters (PHTs) involved in the uptake process of the inorganic forms of As(III and V) [202]. Belonging to the group of aquaglyceroporins are NIPs (Nodulin 26-like Intrinsic Proteins) which participate in a selective import of As(III) and not As(V) to the xylem vessels from the external medium [22,27]. In the case of phosphate transporters, the similarity between As(V) and phosphate and their affinity for phosphate transporters led to genetic approaches based on the knockdown or knockout of the genes involved in phosphate transporters to develop As tolerant crops [19]. Vacuole transporters are also of crucial interest in the establishment of As tolerant crop varieties, since they are involved in the restriction of As movement in a plant through the complexation of As(III) with PC into storage organelles like vacuoles. ATP binding cassette (ABC) transporter family members such as ABCC1 and ABCC2 are included in this group of As transporters [29].

Arsenate reductase are enzymes involved in the conversion of As (V) to As (III) in plants and the overexpression of the genes involved in this enzymatic activities are particularly relevant to improve the As tolerance of crops. Some of these genes are arsenate tolerance QTL1 (ATQ1) [203], and high As content 1 (HAC1) and HAC4 [204,205].

Genetic engineering approaches with glutaredoxins are also required to regulate the redox status of the cells against As toxicity [206]. These cysteine rich proteins are able to reduce the disulphides through reduced GSH [72].

The detoxification of As toxicity in plants is carried out through sequestration with GSH and phytochelatins due to the high affinity of sulfhydryl (-SH) groups of these compounds with As or vacuolar sequestration [22,207]. Glutathione S-transferases are responsible of the reduction of oxidative damage in cells conjugating reactive molecules with GSH [208]. These enzymes through the conjugation process of thiol group of GSH with electrophile substrates can reduce the toxicity in cells sequestering these reactive substrates in vacuoles or being effluxed from cells through ATP dependent pumps [209]. Phytochelatins are vacuolar transporters involved in the sequestration of metalloids such as As into the vacuole, therefore, the establishment of transgenics crops with upregulated genes expression involved in metal resistance are of special interest [210]. It is necessary to point out that the biosynthesis of phytochelatins and GST are dependent on sulphate uptake and conversion to cysteine [211].

Beside to the above-mentioned key genes involved in As tolerance, transcription factors are also considered crucial in the tolerance against this metalloid. Several examples include Zinc-Finger type [212]; bZIP [30]; GeBP-LIKE 4 (GPL4) [213]; NAC [214]; R2R3-type MYB [215]. Moreover, kinases responsible for the regulation of the transcription process like mitogen activated protein (MAP) kinase, SNF1-related kinases (SnRKs) and leucine-rich repeat receptor-like kinase VIII (LRR-RLK VIII) are strengthened in genetic engineering approaches in crops with higher tolerance to As [199].

Several examples about genetic engineering strategies above mentioned carried out in different species to improve the tolerance to As are included in Table 5.

**Table 5.** Genetic engineering approaches for As tolerance and redox and metabolite changes.

Gene Transformed	Product	Donor Species	Recipient Species	Redox and Metabolite Changes	Reference
<i>TaNIP2;1</i>	Silicon channel type transporter	<i>Triticum aestivum</i>	<i>Arabidopsis thaliana</i>	Increase in POD and CAT activities and lipid peroxidation	[216]
<i>WNK1</i>	Serine/threonine protein kinase	<i>O. sativa</i>	<i>A. thaliana</i>	Increase in SOD, POD, and CAT activities	[217]
<i>PRX38</i>	Class III peroxidase	<i>O. sativa</i>	<i>A. thaliana</i>	Increase in SOD, PRX and GST activity and low H <sub>2</sub> O <sub>2</sub> content	[218]
<i>GrxC2.1; GrxC7</i>	Glutaredoxin	<i>O. sativa</i>	<i>A. thaliana</i>	Rise in GSH content and depletion in GSSG content	[219]
<i>PCS1</i>	Phytochelatin synthase	<i>Arabidopsis thaliana</i>	<i>Nicotiana tabacum</i>	Increase in GSH content	[220]
<i>MYB40</i>	Transcription factor in As resistance	<i>A. thaliana</i>	<i>A. thaliana</i>	Increase in thiol-peptide accumulation	[221]
<i>GSTU5</i>	Glutathione S-transferase	<i>O. sativa</i>	<i>O. sativa</i>	Increase in SOD and PRX activity	[222]
<i>SULTR1;2</i>	Sulfate transporters	<i>A. thaliana</i>	<i>A. thaliana</i>	Reduction in GSH content in shoots and roots	[223]
<i>CLT1</i>	CRT-like transporter	<i>O. sativa</i>	<i>O. sativa</i>	Decrease in GSH, GSSG and $\gamma$ -glutamylcysteine levels	[92]
<i>VPT1</i>	Vacuolar Phosphate Transporter 1	<i>A. thaliana</i>	<i>A. thaliana</i>	Increase in anthocyanin level	[224]
<i>Cyc07</i>	40S ribosomal protein S3Ae	<i>Nicotiana tabacum</i>	<i>N. tabacum</i>	Augmentation in SOD, CAT and GR activities	[225]

## 9. Conclusions

Arsenic toxicity is a serious issue as it is not only being uptaken by human through drinking water but also uptaken through plants and animals through the food chain. The productivity of plants is also hampering due to As toxicity. There are hundreds of unanswered questions in the mechanism of As uptake, efflux, translocation, accumulation and detoxification in plants. Only few membrane proteins/transporters have identified in very few plant species. Some research findings proved that As use same transporters [e.g., aquaporins, AQPs: OsNIP (Lsi1, Lsi2; phosphate transporter, OsPHT)] with some other elements. There might be other transporters which should be identified through intrinsic research. Those research findings can be vital for selecting exogenous phytoprotectants/fertilizers which may reduce As uptake by root and then translocation to the following parts of the plants. Mechanism of transportation of As through vascular tissue is not explored completely. The mechanisms and pathways how the As cause oxidative stress that should be focused in diverse way. Plants with enhanced antioxidant defense system under As stress should be recognized and those should be incorporated in various plant improvement programs. Finding out microorganisms and allelochemicals releasing plants which can bind and reduce the As uptake of desired crop can be taken under consideration. Identifying the As hyperaccumulation plants from nature is necessary. Very little is known about the mechanism of As transport and accumulation in different crops/plants including the As hyperaccumulator and non-hyperaccumulator. Then, it will possible to cleanup As contaminated soil, to develop As tolerant plants through breeding, biotechnological or transgenic approaches which will prevent As-induced crop productivity loss and will ensure safe food production for animal or human being. Proteomics, genomics, micromics, transcriptomics, metabolomics, inomics, metallomics approaches can be useful tools for thoughtful realization of the mechanisms of plant response and tolerance to As stress.

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