Plant Molecular Biology Reporter
https://doi.org/10.1007/s11105-021-01280-z

REVIEW

Allantoin: Emerging Role in Plant Abiotic Stress Tolerance

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Received: 22 March 2020 / Accepted: 5 January 2021

Abstract
Allantoin is an intermediate product of purine catabolic pathway that helps in nitrogen mobilization in plants. It is ubiquitously present in the plant kingdom and serves as an important N form transported from source to sink. During the recent years, allantoin has emerged as a molecule involved in increasing stress tolerance in plants. Higher allantoin biosynthesis and accumulation in plants is correlated with an increase in different abiotic stress tolerance such as drought, salt, cold, heavy metals and irradiance. Increased allantoin accumulation subsequently activates ABA (abscisic acid) biosynthetic genes which in turn activate its hallmark downstream stress-related genes such as *RD26* and *29* (response to desiccation), *CAT2* (catalase2), *Mn/Fe/Cu/Zn* superoxide dismutases and *SOS1* (salt overly sensitive 1). External application of allantoin on plants acts as signalling molecule that induces a complex crosstalk between ABA and JA (Jasmonic acid) pathway resulting in increased stress tolerance in plants. Recently, allantoin has been attributed to the role of kin recognition in plants, which highlights its role as a signal molecule that facilitates inter-plant interactions. In this review, we present the up to date understanding of this Nitrogen carrying compound, which has recently emerged as a molecule that plays important roles in abiotic stress tolerance in plants.

Keywords Abiotic stress · Hormones · Purine metabolism · Reactive oxygen species · Signal molecule · Ureide permease

Introduction

Plants, in their life time, are exposed to various environmental stresses and therefore have developed various mechanisms to survive. Different stress conditions may trigger different molecular, biochemical, and physiological processes (Mittler 2006) or else alter the already existing biochemical pathways via upregulation of key enzymes in order to counter these situations (Kaur et al. 2008, 2012; Saxena et al. 2013; Salvi et al. 2016). The upregulation of key enzymes in response to the stress results in the rapid accumulation of several molecules/metabolites throughout the plant that directly or indirectly prepares the plant to fight against the stress arisen. Several such molecules/metabolites have been discovered and their roles in combating stress have been established. However, the role of plant metabolite known as allantoin in modulating stress responses in plants has just began to emerge. Allantoin is already a popular and commercially important compound that has many applications in the cosmetic and pharmaceutical industries (Thornfeldt 2005; Gottschalck and Bailey 2008; Becker et al. 2010; Savić et al. 2015).

Presence of allantoin in plants was established more than 100 years ago and it was almost 80 years later when it was discovered that allantoin plays several important roles in nitrogen transport through the xylem stream. Allantoin is a heterocyclic nitrogenous compound which is ubiquitously present in plant kingdom and it is an intermediate product of purine catabolism. Structurally, allantoin is 1-(2,5-dioxoimidazolidin-4-yl) urea, also known as 5-ureidohydantoin. Allantoin and its immediate hydrolysed form allantoate are collectively known as ureides. Both the molecules are important forms of nitrogenous compounds (carbon/nitrogen ratio of 1:1) that are transported in plants from source to sink (Baral et al. 2016; Desimone et al. 2002; Pélissier and Tegeder 2007). In legumes, it accounts for 90% of the total nitrogenous compound that are mobilised inside the plant tissue, whereas, in non-legume plants, ureides

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Published online: 14 January 2021

constitute only 15% of the total nitrogenous compound. The ureide mode of nitrogen transport through the plant appears to be more efficient than the amide form (asparagine and glutamine) because of its lower carbon to nitrogen ratio and the ability to release four molecules of ammonium per molecule of allantoin upon its complete breakdown (Sagi et al. 1998; Todd et al. 2006; Watanabe et al. 2014a). Therefore, plants utilise allantoin as a sole source of nitrogen during short-term deficiency of soil nitrogen (Desimone et al. 2002; Lee et al. 2018). The concentration of ureides in the stem or xylem ranges between 10 and 20 mM (Layzell and Larue 1982; Rainbird et al. 1984). However, recent reports suggest that allantoin concentration inside the plant increases under different stress conditions such as salt (Shabala et al. 2016; Irani and Todd 2018), drought (Alamillo et al. 2010; Irani and Todd 2016), osmotic stress (Watanabe et al. 2014a), high irradiance (Malik et al. 2016; Irani et al. 2018) and heavy metal stress (Nourimand and Todd 2016, 2017). The increased accumulation of allantoin in plants during stress conditions indicates that allantoin is an important modulator of stress in plants. The present review describes the roles of this essential plant metabolite that has recently emerged as an important stress modulator in plants.

Allantoin Metabolism and Transport

Ureide metabolism consisting of allantoin and allantoate biosynthesis in plants has been reviewed by Werner and Witte (2011). However, here, we briefly discuss the allantoin metabolism in connection to its emerging role in stress signalling in plants. Allantoin biosynthesis in plants utilises purine nucleotides as a precursor via any of the two cellular pathways: (i) de novo synthesis which is the major pathway in the nodules of leguminous plants due to the presence of large amounts of nitrogenous compounds such as glycine, glutamine, aspartate and tetrahydrofolate and (ii) by using fragmented nucleotides available via salvage pathway in non-leguminous plants where nitrogenous compounds are limited inside the tissue (Schubert 1986). In both these pathways, the allantoin biosynthesis begins with the degradation of purines adenosine monophosphate (AMP) and guanosine monophosphate (GMP). AMP is converted into inosine monophosphate by AMP deaminase which is further converted into xanthine via inosine and hypoxanthine while the GMP is converted into guanosine by 5′-nucleotidase which ultimately forms xanthine via xanthosine (Ashihara et al. 2018) (Fig. 1).

In the presence of enzyme xanthine dehydrogenase, xanthine is converted into uric acid in the cytoplasm. From cytoplasm, uric acid is imported into the peroxisomes where it is oxidised by urate oxidase into an unstable product, hydroxyisourate (HIU). This HIU gets converted into L-2-oxo-4-hydroxy-4-carboxy-5-ureidoimidazoline (OHCU) in the presence of enzyme HIU hydrolase. OHCU is also an unstable compound which is hydrolysed immediately into stable product S-allantoin. The enzymes HIU hydrolase and OHCU decarboxylase function as a single bifunctional enzyme called as allantoin synthase (Kim et al. 2007). Pessoa et al. (2010) revealed that allantoin synthase is a tetrameric enzyme which consists of two active sites for HIU hydrolase and four active sites for OHCU decarboxylase. Two stereospecific isomers of allantoin have been reported, namely, R-allantoin and S-allantoin. While R-allantoin is a product of incomplete oxidation of urate by urate oxidase (Cendron et al. 2016), S-allantoin is the predominant biologically active form in plants, which is further converted into allantoate by the enzyme allantoinase that resides in the endoplasmic reticulum. The amino acid residues isoleucine, alanine, histidine, glutamate and arginine present in the active site of allantoin synthase play an important role in hydrolysis as well as decarboxylation of the substrate to produce stereospecific S-allantoin (Cendron et al. 2016). However, whether this allantoin is stored in peroxisomes or endoplasmic reticulum or it moves to some other cellular location needs to be investigated. Further, what triggers allantoin for degradation to allantoate or else for transportation to various other tissues remains to be determined.

In legumes, allantoin transportation may occur through either symplastic or apoplastic routes. In the symplastic route, the allantoin is transported from nodules to the surrounding non-nodulated cells through inner cortex and endodermis via plasmodesmatic connections, whereas the apoplastic route of transportation occurs from nodules to xylem (Näsholm et al. 2009; Tegeder and Rentsch 2010). However, the apoplastic ureide transport is hindered by the casparian strip; therefore, the transportation is supported by plasma membrane-bound transporters known as ureide permease (UPS). UPS transporters are known to be secondary active transporters and are mainly found in the inner cortex of nodules, vascular bundles, outer cortex, and sclereid layers of soybean, French bean, and rice (Desimone et al. 2002; Pélissier et al. 2004; Collier and Tegeder 2012; Redillas et al. 2019). These membrane-bound proteins feature ten membrane spanning transmembrane domains with the characteristic "Walker A" motif located inside the cytoplasm (Desimone et al. 2002). In shoot, allantoin is properly distributed through phloem tissues by active loading into sieve elements by UPSs. Although allantoin transport has been studied in more details in the legumes, several UPS transporter coding genes in non-legumes in addition to the legumes have been reported. These include the genes *GmUPS1-1* and *GmUPS1-2* of soybean, *PvUPS1* of French bean, *AtUPS1*, *AtUPS2*, *AtUPS3*, *AtUPS4*, *AtUPS5l*, and *AtUPS5s* of Arabidopsis, and *OsUPS1*, *OsUPS2*,

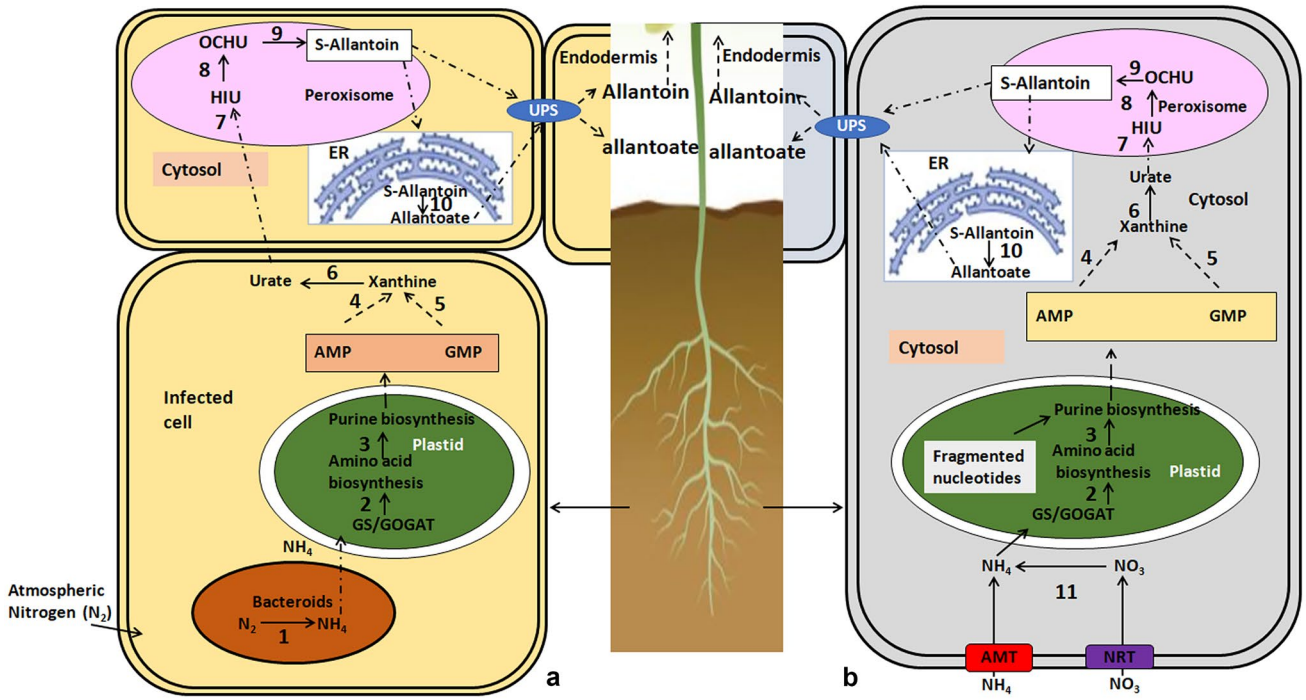

Fig. 1 Schematic representation of (*S*)-Allantoin biosynthetic pathway and its transport through UPS (*Ureide Permease*). **a** In legumes, atmospheric nitrogen is fixed by bacteroides with the help of enzyme nitrogenase (1). Ammonium released from bacteroides is transferred to plastid that is utilized for amino acid biosynthesis through GS/GOGAT (glutamine synthetase/glutamate synthase) (2). (3) Synthesized amino acids are utilized for the biosynthesis of purines adenosine monophosphate (AMP) and guanosine monophosphate (GMP). The enzymes AMP deaminase (4) and 5′-nucleotidase (5), respectively, convert AMP and GMP to xanthine, which is subsequently converted into urate by xanthine dehydrogenase (6) and transported to the nearby uninfected cell. The urate is further transported to the peroxisome where it is converted into intermediate products hydroxyisourate (HIU) by uricase or urate oxidase (7). HIU is converted to L-2-oxo-4-hydroxy-4-carboxy-5-ureidoimidazoline (OHCU) by HIU hydrolase (8). OHCU ultimately form (*S*)-allantoin in presence of enzyme OHCU decarboxylase (9). The (*S*)-allantoin formed in the peroxisome is further transported to endoplasmic reticulum where it is converted into allantoate by enzyme allantoinase (10). **b** In non-legumes, NH_4 required by the GS2/NADH-GOGAT present in plastid for amino acid synthesis is directly supplied by the ammonium transporters (AMT) present in the membranes. The nitrate (NO_3) taken up by the AMT present nitrate transporters (NRT) also present in the cell membranes is first reduced to NH_4^+ by nitrate reductase (11) before its transport to the plastid for amino acid biosynthesis by the GS2/NADH-GOGAT enzymes

and *OsUPS3* of rice (Collier and Tegeder 2012; Pélissier et al. 2004; Pélissier and Tegeder 2007; Desimone et al. 2002; Redillas et al. 2019). Most of the information about the functions of the UPS transporter genes has come from the functional analysis or studies of Arabidopsis *UPS* genes. Schmidt et al. (2004) carried out detailed studies on Arabidopsis UPS family in yeast mutant system *dal4* that is deficient in allantoin uptake. The study revealed variations in the structure and function of the Arabidopsis *UPS* genes. Among the five *UPS* gene products, AtUPS1, AtUPS2, and AtUPS5l were found to have significant affinity for allantoin. AtUPS2 was reported to have the highest affinity for allantoin in Arabidopsis and is localised in the root stele, thus might be engaged during growth on allantoin as a sole nitrogen source. Further, these transporters were also found to be involved in the transport of substrates similar to allantoin such as uracil and other pyrimidine nucleobases (Schmidt et al. 2004, 2006). Gene expression analysis revealed that these different *AtUPS* family members have distinct though overlapping temporal and spatial expressions which make them functionally non-redundant. Whether these transporters play a role in uptake of externally supplied allantoin is still not clear, however, preliminary in vitro studies in *Xenopus laevis* oocytes indicate that allantoin is taken up by a proton coupled transport by AtUPS1 transporter (Desimone et al. 2002).

Recent studies have shown that the expression of UPS coding genes in rice and Arabidopsis is upregulated under nitrogen-deficient conditions. In Arabidopsis, this increase in *UPS* expression has been reported to coincide with increased nitrogen transport from older leaves to younger leaves for their growth (Soltabayeva et al. 2018; Redillas et al. 2019). Moreover, overexpression of *OsUPS1* also leads to higher allantoin accumulation in shoot. Conversely, the knockdown lines of *OsUPS1* revealed dramatic reduction of allantoin accumulation in shoot organs in contrast to the

roots indicating that *OsUPS1* is involved in the transport and partitioning of allantoin throughout the plant (Redillas et al. 2019). UPS transporters have also been studied for their roles in sensing the nitrogen status of plants. Lee et al. (2018) developed molecular nitrogen sensors by fusing rice *OsUPS1* and *OsALN* (*allantoinase*) genes with the luciferase gene. The expression analysis of these genes under variable nitrogen conditions revealed that the plants expressing the *UPS1-LUC2* sensor showed strong luminescence under high internal ammonium and nitrate levels, whereas the plants expressing the *ALN-LUC2* sensor showed strong luminescence under low internal N conditions (< 0.1 mM). As the concentration of ammonium, nitrate, and allantoin determines the nitrogen status of plants, the successful demonstration of this nitrogen sensor embedded in the plant itself has showed its potential applications in precision farming/agriculture.

The UPS transporter family from legumes like soybean and French bean has few members and similar to non-legume transport allantoin and other similar heterocyclic nitrogenous compounds. However, their major role is to transport the ureides synthesised in the nodules to the shoot organs where they are utilised as nitrogen source. Hence, allantoin transport is as important as its biosynthesis for proper distribution of allantoin in different parts of the plants and UPS family members play major roles to facilitate this process.

Ureide Accumulation and Regulation in Developmental Stages

Ureide accumulation is regulated in a tissue and developmental stage-specific manner in nitrogen fixing legumes as well as in nitrate feeding legumes (Díaz-Leal et al. 2012). Several reports suggest that allantoin and allantoate concentrations in all tissues, i.e. root, shoot and leaves of nitrogen fixing and nitrogen-supplied plants, increase as the plant gradually develop from vegetative to reproductive stage. This suggests that allantoin is increasingly needed as a source of nitrogen during active vegetative growth through the reproductive stages due to high demands of nitrogen (Matsumoto et al. 1977; Tajima et al. 2004; Raso et al. 2007; Díaz-Leal et al. 2012). However, the concentrations of allantoin and allantoate vary in the roots of the nitrogen fixing and nitrogen-supplied plants at the reproductive stage. High allantoin and allantoate concentrations with higher activity of allantoin biosynthetic enzyme and urate oxidase were observed in roots of nitrogen fixing plants while the concentrations of both these molecules decreased in the nitrate-supplied plants (Díaz Leal et al. 2012). This might be due to the continuous synthesis of ureides in the roots of the nitrogen fixing plants.

Ureide degradation supports normal growth under nitrogen limiting condition as well as during transition from vegetative to reproductive phase in Arabidopsis (Matsumoto et al. 1977; Nakagawa et al. 2007; Soltabayeva et al. 2018; Takagi et al. 2018). This intact ureide catabolic pathway is needed to support normal growth as mutants affected in purine catabolic enzymes are unable to effectively utilise nitrogen, which result in early flowering. However, Takagi et al. (2018) reasoned that this is probably due to the phytohormone (indole-3-acetic acid and gibberellic acid) disbalance. Ureides also serve as a nitrogen source for young developing leaves in Arabidopsis plants growing under low nitrogen condition. However, when supplied with sufficient nitrate levels, the abundance of ureide catabolic enzymes decreases which was also consistent with the *Atxdh1* (*xanthine dehydrogenase 1*) mutant studies, which is a catalytic bottleneck enzyme in purine catabolism. The *Atxdh1* mutant studies also demonstrated that plant accumulates allantoin under low nitrogen condition (Soltabayeva et al. 2018). Beside this, growth of *Atxdh1* mutant was also hampered more than the wild type under both dark stress (Brychkova et al. 2008) and drought stress conditions (Watanabe et al. 2010) which implicit that allantoin metabolism is essential under different stress condition. Allantoin is also capable of supporting seedling growth as the sole source of nitrogen in plants like Arabidopsis and rice; however, the growth of these plants was found to be slower than that on regular nitrogen sources (Desimone et al. 2002; Lee et al. 2018). This might be due to the fact that the allantoin needs to be degraded first to release the nitrogen for the synthesis of other compounds while the ammonium and nitrate forms of nitrogen are more readily utilised by the plants. Further, the allantoin catabolism is a highly regulated process that depends on the spatial and temporal nitrogen status of the plant. Allantoin, thus, serves as one of the important source of nitrogen for growth and development of the plant and acts as a significant source of nitrogen under nitrogen deficient condition.

Allantoin Accumulation and Regulation in Abiotic Stress Tolerance

Allantoin has been known to function in nitrogen metabolism and transport for decades. However, in recent years, many interesting reports have revealed that allantoin accumulation increases under different abiotic stresses. For example, allantoin content increased in response to various abiotic stresses in Arabidopsis (Lescano et al. 2016), rye (Sagi et al. 1998), barley (Shabala et al. 2016), pea (Corpas et al. 1993), common bean (Khadri et al. 2001; 2006) and halophyte, *Crithmum maritimum* (Ventura et al. 2014) (Table 1). Allantoin accumulation during environmental challenges has been extensively reported in legumes (Corpas et al. 1993; Khadri et al. 2001; Silvente et al. 2012; Khan et al. 2019). However, because of the availability of different mutants of genes involved in purine catabolic pathway, mechanism

Table 1 Stress-induced allantoin accumulation in different plant species under various abiotic stress conditions

	Stress	Plants	Duration of stress	Description	References
1	Drought	Selaginella lepidophylla	Allantoin was measure after 2 days of drought stress	Higher accumulation of allantoin might induce ROS scavenging mechanism	Yobi et al. (2013)
2	Drought	Phaseolus vulgaris	Higher accumulation of allantoin was measured after 7 days and 14 days of drought stress	Higher concentration of allantoin was found in tolerance varieties with deficit nitrogen fixation	Coleto et al. (2014), Alamillo et al. (2010)
3	Drought	Oryza sativa	Drought stress was given for 33 days to measure allantoin accumulation	Metabolite analysis shows higher accumulation of allantoin in tolerance varieties	Casartelli et al. (2018)
4	Drought	Arabidopsis thaliana	Allantoin was measured in wild type after 5 days and 10 days of drought stress[1] Drought stress was given to *aln* mutants for 60 min then allowed to grow under normal condition for recovery then allantoin was quantified[2]	Allantoin accumulation was higher in *aln* mutant than wild type under stress condition to initiate tolerance mechanisms (ABA biosynthesis, ROS activities and other stress responsive genes)	[1]Irani and Todd (2016), [2]Watanabe et al. (2014)
5	Drought	Sporobolus stapfianus	Accumulated allantoin was determined after 15 days of drought stress	Allantoin accumulation increases under stress condition to decrease hyperammonemia condition	Oliver et al. (2011)
6	Drought	Glycine max	Higher accumulation of allantoin was measured by withholding day for 10 days	Allantoin was remarkably increased in tolerant variety under stress	Silvente et al. (2012)
7	Drought	Cicer arietinum	Allantoin was measured after 14 days and 25 days of drought stress	Allantoin accumulation was high in tolerant variety and acts as stress marker	Khan et al. (2019)
8	Salinity	Hordeum vulgare	Salt stress (100 mM NaCl) was given for 4 days to measure allantoin concentration	Exogenous allantoin application inhibits K^+ efflux in root to provide tolerance	Shabala et al. (2016)
9	Salinity	A. thaliana	Allantoin was determined 10 days after salt treatment (100 mM NaCl)[1] Salt stress (75–250 mM NaCl) was given for 14 days to measure allantoin accumulation[2] Salt stress (50–250 mM NaCl) was given for 14 days to measure allantoin accumulation[3]	Allantoin concentration was high under salt stress condition in *aln* mutant, exogenously applied allantoin (0.1 and 1 mM) in wild type plant and *VvXDH* overexpression lines to upregulated stress related genes	[1]Irani and Todd (2018), [2]You et al. (2017), [3]Lescano et al. (2016)
10	Salinity	Lolium multiflorum	Allantoin was measured after 14 days of salt stress (100 mM NaCl)	Allantoin concentration was higher in root under salt stress condition	Sagi et al. (1998)
11	Salinity	Crithmum maritimum	Salt stress (50 and 100 mM NaCl) was given for 14 days to quantify allantoin accumulation	Allantoin accumulation increases along with increasing salt stress	Ventura et al. (2014)
12	Salinity	Pisum sativum	Higher accumulation of allantoin was determined after 14 days of salt treatment (30–300 Mm NaCl)	Higher accumulation of allantoin was found in tolerant variety	Corpas et al. (1993)

Table 1 (continued)

	Stress	Plants	Duration of stress	Description	References
13	Salinity and ABA treatment	O. sativa	Both salt (140 mM NaCl) and ABA (10 µM ABA) treatment was given for 14 days to measure allantoin concentration	ABA treatment along with salt stress increases allantoin biosynthesis in rice varieties. Allantoin serves as stress marker in fourteen rice varieties	[1]Wang et al. (2015), [2]Nam et al. (2015)
14	Salinity and ABA treatment	P. vulgaris	Both salt (100 mM NaCl) and ABA (1 and 10 µM) treatment was given to measure allantoin after 3 days and 6 days[1] Allantoin was measure after salt stress (25–100 mM NaCl) after 3 days, 6 days, 9 days and 12 days[2]	Allantoin biosynthesis increased with external application of ABA under salt stress condition	[1]Khadri et al. (2006), [2]Khadri et al. (2001)
15	Metal	A. thaliana	Metal stress of $CdCl_2$ (0, 500, 1000 and 1500 µM) was implied for 3 weeks to measure allantoin concentration	Allantoin concentration was higher in *aln-3* mutant than Col-0 under Cadmium stress	Nourimand and Todd (2016, 2017)
16	High irradiance	Coffea arabica	Irradiance stress (1000 and 2000 µmol photons m^{-2} s^{-1}) was given for 50 days	Higher irradiance increases allantoin content	Pompelli et al. (2013)
17	High irradiance	Eutrema salsugineum	Allantoin was determined after irradiance stress (250 and 750 µmol photon m^{-2} s^{-1})	Higher concentration of allantoin increases anthocyanin biosynthesis	Malik et al. (2016)
18	High irradiance	A. thaliana	Irradiance stress (250 and 750 µmol photons m^{-2} s^{-1}) was given to determine allantoin at different time interval 4 days, 7 days, 10 days, 14 days and 21 days	Allantoin biosynthesis increases significantly in *aln-3* mutant in comparison to wild type	Irani et al. (2018)
19	Dark stress	A. thaliana	Dark stress (40 µmol photons m^{-2} s^{-1}) was given for 4 weeks to quantify allantoin accumulation	Exogenous allantoin (0.1 mM) application prevents chlorophyll degradation and activate ROS enzyme in *Atxdh* mutant	Brychkova et al. (2008)
20	Osmotic stress	A. thaliana	Allantoin was measure in wild type Arabidopsis after 4 days of salt (200 Mm NaCl) and mannitol stress (200 mM) treatments [1] Osmotic stress (100–200 Mm mannitol) was given for 14 days to determine allantoin[2]	Increased concentration of allantoin provides tolerance to *aln* mutants by activation of stress responsive mechanisms under osmotic stress (mannitol and polyethylene glycol)	[1]Irani and Todd (2016), [2]Watanabe et al. (2014)
21	Cold	O. sativa	Allantoin (1 mmol/L) was applied externally to rice seeds which provide cold tolerance	Exogenous application of allantoin on rice grains provides cold tolerance	Wang et al. (2012)

of allantoin accumulation in plants is studied in the model plant Arabidopsis (Desimone et al. 2002; Hauck et al. 2014; Lescano et al. 2016). The reverse genetics studies with these mutants, e.g. *xdh1* (*xanthine dehydrogenase* mutant), *aln1, aln2* (mutants of *allantoinase*) and *ups* (mutant of *Ureide permease*), showed enhanced allantoin accumulation in these mutants, which is related to better growth under different stress conditions such as salt (Lescano et al. 2016; You et al. 2017), drought (Irani and Todd 2016), heavy metal (Nourimand and Todd 2017) and irradiance (Irani et al. 2018) that are discussed below.

Drought

Drought is the most important abiotic stress which hampers plant growth and development by impairing cellular osmotic potential. Under drought stress condition plants tend to accumulate allantoin in their different organs, e.g. *Phaseolus vulgaris* was found to increase allantoin concentration in different organs, namely leaves, roots, shoots and pods under drought condition (Coleto et al. 2014; Alamillo et al. 2010). The increase in allantoin was correlated with higher activity of its biosynthetic enzyme urate oxidase in these organs (Allamilo et al. 2010). In legumes, the ureide concentration was found to be more in sensitive cultivars than tolerant cultivars under drought stress (Kaur et al. 1985; Rao and Venkateswarlu 1987; Coleto et al. 2014). The compromised activity of ureide catabolic enzymes in these sensitive cultivars might act as a bottleneck for ureide accumulation under drought stress condition which was less affected in tolerant varieties thus maintaining sufficient nitrogen supply under drought (Gil-Quintana et al. 2013; King and Purcell 2001; 2005). However, allantoin along with another nitrogenous compound uridine was found to be accumulated in higher amount in the leaves of drought-tolerant genotypes of rice (N22 and Dular) (Casartelli et al. 2018) as well as *Sesamum indicum* (ZZM3330) (You et al. 2019) than their corresponding sensitive genotypes under water deficit condition. Such kind of genotype-specific induction of metabolites is reported in literature and is contributed mainly by differences in allelic forms of the accountable genes (Majee et al. 2004). Further, metabolite profiling in different plants such as *Sporobolus stapfianus* (Oliver et al. 2011), soybean (Silvente et al. 2012), *Selaginella lepidophylla* (Yobi et al. 2013) and chickpea (Khan et al. 2019) revealed a significantly increased level of allantoin among other metabolites under water deficit conditions. Besides the increment of allantoin under stress condition, the knockdown mutant of xanthine *dehydrogenase* in Arabidopsis (*Atxdh*) showed reduced ROS detoxification under drought stress. Further, the exogenous application of allantoin precursor compound urate also helps in restoring the survival rate of *Atxdh* mutant lines (Watanabe et al. 2010). Therefore, allantoin deficiency or less accumulation compromises the stress tolerance mechanisms (Watanabe et al. 2014b).

Salinity

Salinity is one of the major abiotic stress which hinders the plant growth and hence compromises yield (Molla et al. 2015; Ganie et al. 2019). Increased allantoin content has been considered as a salt stress tolerance marker in rice varieties. Nam et al. (2015) reported that increased allantoin might help in maintaining the biomass of these tolerant varieties under salinity stress. Allantoin accumulation was also found to be increased under salt stress condition in different plant organs such as root of rye (Sagi et al. 1998), leaves of *C. Maritium* (Ventura et al. 2014) and nodules of *P. vulgaris* (Khadri et al. 2001). Allantoin accumulation was also increased in response to salt stress and ABA (abscisic acid) treatment in roots of tolerant and susceptible varieties of rice (PL177 and IR64, respectively); however, accumulation was higher in tolerant genotypes (Wang et al. 2015). Moreover, in the salt tolerant pea cultivar, the activity of urate oxidase was also less inhibited than in the sensitive cultivar under salt stress (Corpas et al. 1993). The allantoin concentration was found to increase in Arabidopsis seedlings after 4 days of salt and mannitol treatments (Irani and Todd 2016). All these experiments indicate that allantoin is involved in long-term stress tolerance mechanisms in some plants. However, our experimental data shows that allantoin accumulates 1.25-fold starting within 1 h of salt treatment and remains high till 4 days in rice seedlings indicating that it also represents an early response mechanism to salt stress (unpublished data). Such increase in allantoin concentration has not been reported at early time points in Arabidopsis (Irani and Todd 2016), suggesting that allantoin accumulation in different plant species needs to be determined at early time points of stress in order to achieve better insight about allantoin accumulation due to salinity stress. The reason for this variable response is, however, not clear, but differential regulation of allantoin accumulation in monocots (rice) and dicots (Arabidopsis) might contribute to this. Additionally, exogenous application of allantoin at concentrations as low as 0.1 mM and 1 mM also provides tolerance to 1-day-old Arabidopsis seedlings against salt stress, which was associated with accumulation of allantoin in low concentration of nanomole per mg fresh weight (Irani and Todd 2018). Interestingly, *aln1* and *aln2* mutants of *allantoinase* gene (which functions to metabolise allantoin to allantoate) in Arabidopsis that shows higher accumulation of allantoin were found to be tolerant to salt treatment in addition to other abiotic stresses (Watanabe et al. 2014a; Lescano et al. 2016). The over expression of the *xanthine dehydrogenase* gene from *Vitis*

vinifera in Arabidopsis confirmed salt stress tolerance in the transgenic lines that showed increased allantoin and proline concentration under salt stress (You et al. 2017). Thus, taken together, allantoin accumulation under salt stress condition in different plant species clearly suggests its role in salt stress tolerance.

Heavy Metal Stress

The industrial activity such as mining, unchecked use of inorganic fertilizers, pesticides, and other chemical application on soil increases the level of hazardous metals, e.g. cadmium, zinc and lead. The plant growth is severely hampered by these metals. Allantoin accumulation in plants has also been found to increase tolerance against heavy metal stress, e.g. in Arabidopsis, cadmium-induced heavy metal stress triggered higher accumulation of allantoin (Nourimand and Todd 2016, 2017). Furthermore, a higher level of *urate oxidase* expression in the Arabidopsis *aln-3* mutant has been observed in response to metal stress, which displayed better tolerance towards Cd levels up to 1500 µM (Nourimand and Todd 2017). The *aln-3* mutant roots also showed higher activities of ROS (reactive oxygen species) scavenging enzymes like superoxide dismutase (SOD), catalase (CAT) and ascorbate peroxidise (APX) than wild-type roots when treated with $CdCl_2$ (Nourimand and Todd 2017). Except Arabidopsis, no other plants have been studied to understand the role of allantoin accumulation under metal stress. As heavy metal toxicity is an emerging problem in the Agri-ecosystems, such studies in crop plants on other heavy metal stresses would aid in designing effective strategies to overcome it.

Irradiance Stress

High irradiance causes damage to the photosystem II during photosynthesis which is known as photooxidation of green plants. In addition to other abiotic stresses, high irradiance has also been shown to increase allantoin accumulation in *Coffea arabica* (Pompelli et al. 2013), *Eutrema salsugineum* (Malik et al. 2016) and more recently in Arabidopsis (Irani et al. 2018). The *aln-3* mutant of Arabidopsis which significantly accumulates higher levels of allantoin but lower levels of anthocyanin was more tolerant to irradiation stress in comparison with the wild type. The mutant plants showed better growth in both moderate as well as in high irradiance conditions (Irani et al. 2018). The higher level of allantoin accumulation and less amount of anthocyanin accumulated during irradiance in *aln-3* mutant clearly indicated the important role of allantoin in irradiance stress tolerance (Irani et al. 2018).

Dark Stress

Light is an essential factor for photosynthesis in plants; under low light condition, the photosystems are severely affected. The dark stress causes chlorosis of leaves as well as decrease in biomass in addition to other symptoms. Interestingly, the *Atxdh* mutant line that is defective in allantoin biosynthesis had reduced growth, increased chlorophyll degradation and higher accumulation of ROS compounds compared with wild type under dark stress. External application of allantoin (0.1 mM) increases the ROS scavenging activity in this mutant, which suggests its possible role in ROS detoxification (Brychkova et al. 2008; Wang et al. 2012).

All the studies described above underline the accumulation of allantoin during various abiotic stresses right from the lower plants (e.g. *S. stapfianus* and *S. lepidophylla*) to higher plants as well (e.g. *Oryza sativa*, *Glycine max* and *Arabidopsis thaliana*) (Oliver et al. 2011; Yobi et al. 2013; Lescano et al. 2016; Lee et al. 2018). Studies on Arabidopsis *aln* and *xdh* mutants have revealed that allantoin accumulation could be activated by multiple abiotic stresses. This might be due to the overlapping nature of various abiotic conditions, which is more relevant to plants in their natural habitats where they might experience more than one type of stress at any particular time. Activation of allantoin accumulation in response to multiple stresses suggests that allantoin might function as an important stress tolerance inducer or a signalling molecule that is evolutionarily conserved in plant kingdom.

Role of Allantoin in Abiotic Stress Tolerance in Plants

Allantoin accumulation during abiotic stresses among different plant groups highlights its stress responsive requirement in the tissues. Many studies have revealed that abiotic stress responsive allantoin accumulation in Arabidopsis is attributed to reduced expression of the allantoin degrading enzyme gene, *allantoinase* and simultaneously increased expression of the allantoin biosynthesis enzyme gene, *uricase* (Irani and Todd 2016; Lescano et al. 2016; Nourimand and Todd 2016, 2017; Irani et al. 2018). However, few studies have delved deeper into the mechanisms involved in this increased allantoin concentration and the corresponding stress tolerance demonstrated by the plants.

Allantoin has been speculated to function via different mechanisms in the last two decades, where it has been described as an antioxidant or a signalling molecule (Gus'kov et al. 2004; Brychkova et al. 2008; Watanabe et al. 2014a). Several studies suggested that allantoin may

function as another antioxidant because of its direct effect on limiting ROS-mediated oxidative injury in bacteria as well as plants under in vitro conditions (Gus'kov et al. 2004; Brychkova et al. 2008).Under in vivo conditions, higher allantoin accumulation in Arabidopsis *aln* mutant has showed increased expression of several ROS pathway genes, e.g. *SOD* and *APX* with concomitant increase in free radical scavenging activity (Nourimand and Todd 2016). Interestingly, this increased allantoin, whether accumulated in vivo or externally applied, has been shown to reduce the endogenous H_2O_2 and O_2^- concentrations under salt stress (Irani and Todd 2016; Watanabe et al. 2010). In animals also, allantoin has been known to positively regulate the antioxidant pathways (Gus'kov et al. 2001). Exogenous application of allantoin at physiologically very high concentrations on rice has been reported to increase in ROS activity. However, there was no evidence of allantoin acting as a direct quencher of free radicals or affecting lipid peroxidation indicating that it might act as a signalling molecule (Wang et al. 2012). Thus, the difference in experimental evidence regarding the role of allantoin in initiating ROS-mediated stress tolerance among rice and Arabidopsis needs further detailed analysis to be able to comment on the possible overlapping mechanism of action regarding allantoin which might involve ROS enzymes.

Nevertheless, the current evidences suggest that it should be unlikely that allantoin works as a functional metabolite such as proline which imparts stress tolerance by accumulating at significantly high concentrations in the plants under such stresses. A series of studies where allantoin quantification has been performed under stress conditions (Allamillo et al. 2010; Nam et al. 2015; Shabala et al. 2016; Khan et al. 2019) underline that allantoin accumulation occurs at physiologically low concentrations. Phenotypic effects of externally applied allantoin under salt stress also achieve saturation beyond a certain concentration (Irani and Todd 2018), which might act as a threshold value. Thus, when this concentration is achieved, the downstream stress responsive machinery of the cell is sensitised to take over. Watanabe et al. (2014a) reported that this kind of a threshold value for allantoin accumulation might prime the plants for a more rapid and pronounced stress response.

Although several mechanisms of allantoin-mediated stress protection have been assumed, the most extensive work till date on the role of allantoin in stress protection has been done by Watanabe et al. (2014a). The group studied the global transcriptome of the *aln* mutants and revealed increased transcription of stress-related genes with corresponding tolerance towards drought as well as osmotic stress. They also showed that several stress-inducible ABA-regulated genes were triggered under water deficit condition. Allantoin accumulation in the *aln* mutant was also shown to stimulate ABA biosynthesis even in absence of any stress by positively regulating NCED3(9-cis-epoxycarotenoid dioxygenase), which is an important ABA biosynthetic enzyme that participates in the activation of β-glucosidase homolog 1 (BG1) to hydrolyse glucose-conjugated ABA into its active form. Further experiments in ABA biosynthesis deficient mutant, *aba 2–1* and in BG1 deficient mutant, *bglu18*, suggested that allantoin-mediated ABA increase requires functional ABA biosynthesis as well as its deconjugation pathways (Watanabe et al. 2014a).

In Arabidopsis, roots accumulate more allantoin than shoots under both control as well as salinity stress but the increment was more under salt stress condition. From roots, it is transported to shoots suggesting an important role of stress responsive signalling. Additionally, promoter studies of *AtALN* also revealed a transcriptional inactivation of the allantoinase gene under salt stress to accumulate higher concentration of allantoin (Lescano et al. 2016, 2020). AtUPS5, which is a member of allantoin transporter protein family in Arabidopsis (Desimone et al. 2002), was found to be induced under salt stress and the mutant for this gene displayed salt sensitivity indicating the essential requirement of allantoin during salt stress. Detailed studies on this transporter suggested that AtUPS5 may serve as a critical component essential for allantoin transport leading to its consequent accumulation in root under salt stress (Lescano et al. 2016, 2020).

Interestingly, the promoter regions of *urate oxidase* scanned by PlantCARE in Arabidopsis and rice were found to be enriched in abiotic stress responsive *cis* elements like *ABRE* (*abscisic acid-responsive element*), *DRE1* (*dehydration-responsive element*), *LTR* (*low-temperature responsive element*) and *MBS* (*MYB binding site*), thus, suggesting abiotic stress-regulated transcriptional control of allantoin biosynthesis. Collectively, it appears that these effects of allantoin might be ABA mediated through the induction of genes involved in ABA biosynthesis and deconjugation. As ABA is a major stress signalling hormone that modulates a battery of downstream defence responsive genes, it would be tempting how allantoin induces ABA biosynthesis genes.

The current set of evidence indicates that allantoin is not needed at physiologically very high concentrations to induce its effect on stress tolerance mechanisms. Therefore, it might act as a stress signalling regulatory compound that regulates the transcription of many stress-induced genes such as those

coding for ROS pathway enzymes or other genes in a ROS-independent pathway.

Crosstalk of Allantoin with Other Stress Signalling Pathways

Plants perceive signals for both biotic and abiotic stress conditions through different signalling compounds such as ethylene, glucose, salicylic acid (SA) and Jasmonic acid (JA). As discussed in the previous section, allantoin is also speculated to work as a signalling molecule, effective even in small concentrations to activate other stress responsive pathways and their downstream genes (Fig. 2). ABA is a major phytohormone and crucial in abiotic stress signalling in all plants. Various abiotic stresses such as salt, dehydration and cold exhibit similar genetic and physiological responses in plants and are regulated by ABA-dependent signalling pathways (Tuteja 2007). Membrane receptors like ion channels, histidine kinase or receptor like kinase first perceive these stress signals and then the secondary signal molecules such as Ca_2^+, inositol phosphates, ROS or ABA take over from there to kick off more intricate signalling cascades (Tuteja 2007).

Similarly, allantoin induces ABA biosynthesis via regulating transcription of ABA biosynthesis pathway genes and release of ABA from its conjugated glucosyl ester form in plants. Exogenously applied allantoin also induces the expression of *NCED3*, *RD29A*, *RD29B*, *RD26* and salt overly sensitive (SOS) pathway gene (*SOS1*) and increased ABA accumulation in Arabidopsis (Watanabe et al. 2014a). However, ABA mutants, *aba 2-1* and *bglu18* defective in

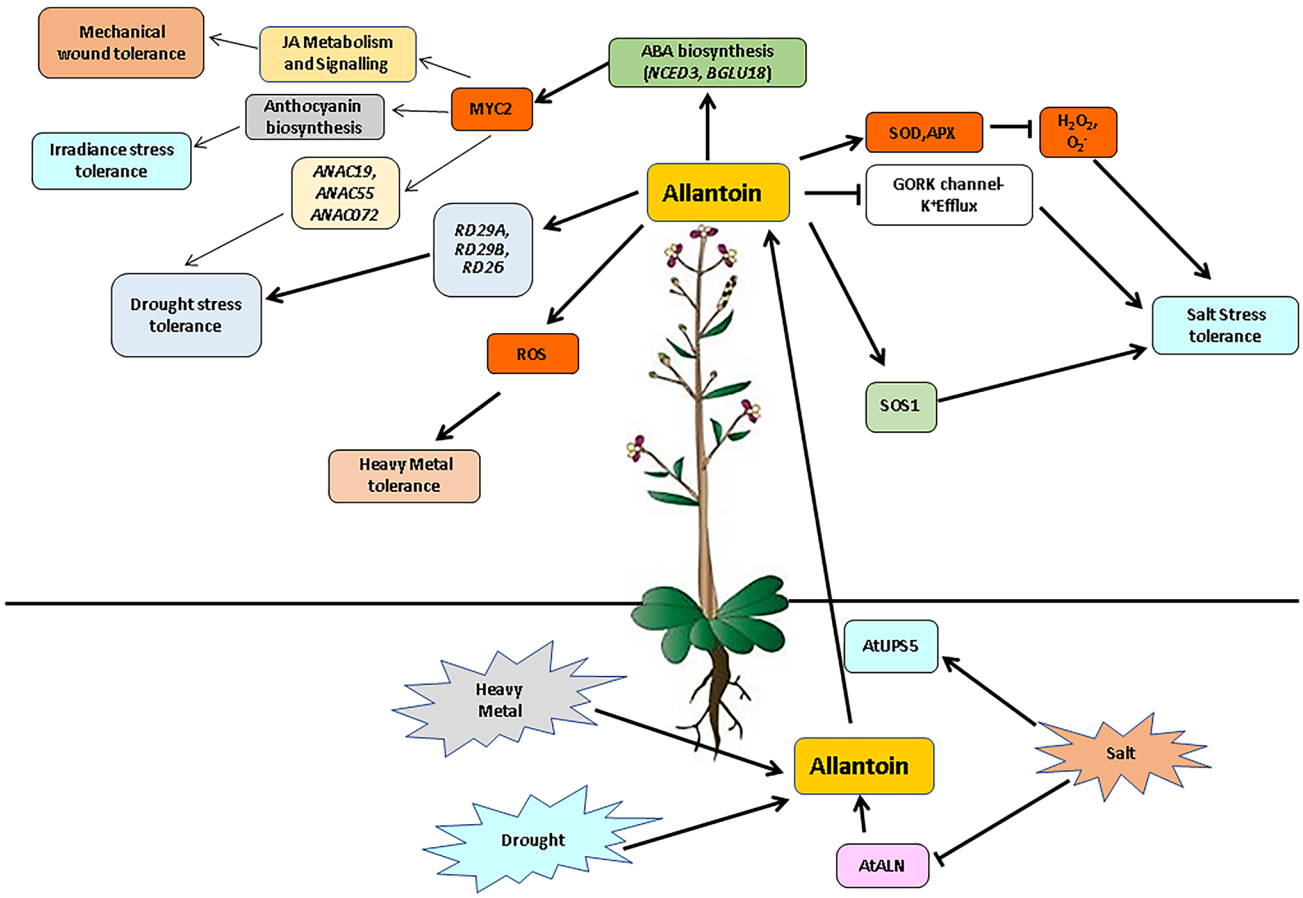

Fig. 2 Mechanistic representation of allantoin-mediated abiotic stress response and interaction with major plant hormone pathways. Allantoin accumulates in plant root via transcriptional suppression of its degrading enzyme allantoinase (ALN) during various abiotic stress and is transported to the aerial part through UPS (ureide permease) where it activates many known intermediate stress pathway genes and hormones for offering stress tolerance (ABA: abscisic acid, APX: ascorbate peroxidase, SOD: superoxide dismutase, GORK: guard cell outward-rectifying potassium channel, SOS1: salt overly sensitive 1, ROS: reactive oxygen species, MYC2: basic-helix-loop-helix transcription factor, JA: Jasmonic acid, ANAC19/ ANAC072: abscisic-acid-responsive NAM, ATAF and CUC transcription factor and RD29A, 29B and 26 (response to desiccation)

ABA production when exposed to exogenously supplied allantoin, failed to increase the transcripts of these genes along with ABA levels thus endorsing the idea that allantoin-induced stress response is routed through ABA-mediated pathways (Watanabe et al. 2014a). Transgenic Arabidopsis overexpressing *XDH* gene from *V. vinifera* resulted in enhanced allantoin concentrations which in turn also showed salinity tolerance via activation of ABA signalling pathway which ultimately enhances ROS scavenging (You et al. 2017). Microarray analysis in Arabidopsis *aln* mutant demonstrated that increased allantoin stimulates both ABA- and JA-mediated responses (Takagi et al. 2016). As ABA also stimulates the MYC family genes (transcription factors MYC2/3/4), which trigger the activation of JA and jasmonoyl-l-isoleucine biosynthesis but inhibits the ethylene-regulated ERF and SA, indicates that allantoin first induces ABA biosynthesis.

The JA signalling pathway canonically provides tolerance to mechanical wounding (Anderson et al. 2004; Fernández-Calvo et al. 2011; Niu et al. 2011) and oxidative stress as well as it regulates the anthocyanin biosynthesis and root growth inhibition (Lorenzo et al. 2004; Wasternack and Hause 2013). The higher concentration of allantoin in *aln-1* mutant of Arabidopsis stimulates MYC-targeted genes such as NAC transcription factors (*ANAC019*, *ANAC055*, *ANAC072*), *VEGETATIVE STORAGE PROTEIN 1*, *SABATH METHYLTRANSFERASE* and *SALICYLIC ACID GLUCOSYLTRANSFERASE1* which act as repressors of the SA signalling. Higher expression of the allantoin-induced JA-pathway genes in *aln* mutant was also reported such as 13-*LIPOXYGENASE-LOX3/LOX4*, *JASMONATE ZIM-DOMAIN-JAZ3/JAZ4*, *ALLENE OXIDE SYNTHASE*, *ALLENE OXIDE CYCLISE 1*, *OXOPHYTODIENOATE REDUCTASE*, *JASMONATE-AMIDO SYNTHETASE*, *CYTOCHROME P450 MONOOXYGENASE 94B3* and Jasmonate-associated myc2-like1 repressor proteins (Takagi et al. 2016). The ABA deficient (*aba2-1* and *bglu18*), JA insensitive (*jar1-1*), MYC2 deficient (*myc2-3*) mutants were also unable to activate JA signalling genes upon external application of allantoin suggesting that allantoin functions via a coordinated network of these hormones and there is a larger crosstalk among ABA, MYC and JA signalling where allantoin may serve as a regulatory molecule which regulates the stress responses in the plants (Takagi et al. 2016) (Fig. 2).

Recently, allantoin has been endowed with an interesting role in kin recognition, where the roots of the rice lines when grown with distantly related lines displayed increased allantoin secretion and as a result better growth in terms of root biomass in comparison with growth with similar lines or cultivars. Incidentally, this function of allantoin was found to be mediated through the regulation of auxin biosynthetic enzymes such as OsYUCCA3, OsYUCCA4 and OsYUCCA6 as well as auxin transporters OsPIN1, OsPIN2 and OsAUX1 (Yang et al. 2018). The use of various hormone biosynthesis and signalling mutants has provided definite evidence on the involvement and crosstalk of these hormone and their signalling pathways with that of allantoin-mediated abiotic stress responses (Takagi et al. 2016). However, further detailed experiments will be useful to elucidate the master regulators of these stress-induced allantoin-mediated signalling cascades.

Conclusions and Future Perspectives

Allantoin has been studied since early twentieth century for its role in nitrogen mobilization in plants, especially legumes. Recent studies have revealed its promising role in stress responses in various plants. However, detailed studies exploring the role of allantoin in abiotic stress regulation have been performed in the model plant Arabidopsis only but many other species of plants have been shown to share this tolerance with concomitant allantoin accumulation to various abiotic stresses such as salt, drought, heavy metal and irradiation stress. Similar studies in other plant species will shed more light on the universality of this allantoin-induced stress response among plant kingdom. In-depth study is also required to understand whether ureide pathway is the sole source of precursor for allantoin biosynthesis as the *xdh1* mutant in Arabidopsis also accumulates some amount of allantoin indicating that an alternative gene or pathway may exist. In this situation, a thorough genetic study is warranted to uncover any QTL (Ganie et al. 2019) which might be involved in allantoin biosynthesis. Apart from that with the present understanding about eukaryotic gene expression, there could be some noncoding RNA such as miRNA (, Becker et al. 2010), long-noncoding RNA or circRNA that may involve in the allantoin biosynthetic pathway which need to be looked in to. Initial experimental evidences suggest that allantoin does not function as a metabolite and both the susceptible and tolerant plant varieties accumulate allantoin as a response to stress albeit at variable levels which indicates that in tolerant varieties, allantoin possibly accumulates and reaches a threshold level which is required to initiate its role in abiotic stress signalling which are further amplified by the stress signalling hormones such as ABA and JA. Allantoin also regulates the overall expression of stress-related genes like ROS pathway genes and *SOS*; however, few studies suggest otherwise but there is a possibility of allantoin acting via both ROS-dependent and ROS-independent pathways to present stress tolerance that needs to be investigated for further understanding. On an interesting note, not only allantoin stimulates ABA biosynthesis but ABA also induces the transcripts of allantoin biosynthesis genes; therefore, further studies to

elucidate this possible feedback mechanism of regulation between the genes of these two pathways would provide significant details.

Allantoin content has also been utilised for screening stress-tolerant varieties in soybean, chickpea and rice and can be used as a stress marker in these species. For a deeper understanding of the regulatory roles of allantoin, we also need to understand the transcriptional and translational control of genes involved in allantoin biosynthesis and transport which includes the critical study of the promoter region of the key genes encoding urate oxidase, allantoin synthase and UPS transporters which will help us to identify the relevant *cis*-elements and to understand their regulation under different stress conditions. Additionally, the differences between the coding sequences of allantoin biosynthesis genes and their effects on the enzyme activities between tolerant and susceptible varieties will also provide key information regarding the stress-tolerant orthologs of these genes which can be used for further introgression into the susceptible varieties either through conventional approaches or genetic engineering technologies.

Acknowledgements We are grateful to Director, ICAR-NIPB for his support and valuable suggestions.

Funding HK and SC received the financial support from DST-Inspire Faculty grant and Council of Scientific and Industrial Research, respectively.

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