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Trehalose: A Key Player in Plant Growth Regulation and Tolerance to Abiotic Stresses

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Abstract

Plant abiotic stresses endanger crop production and food security to a growing degree under the present climate change scenario. This calls for effective measures to be deployed to increase the level of agricultural production to meet the needs of soaring world population. Application of osmo-protectants and soluble sugars reported to counter abiotic stresses in many crop species. Trehalose (Tre) is one such non-reducing sugar found in bacteria and yeasts, where it serves as source of carbon, and in higher plants and animals, where it acts as osmo-protectant. Tre is involved in various physiological, biochemical and molecular mechanisms associated with plant growth, development and defense against drought, salinity, cold, heat, UV rays, nutrient deficiency and heavy metal stresses. It helps plants maintain cellular integrity under stress by upgrading the antioxidant defense system. However, Tre amounts are lower than those needed to assure adequate plant stress tolerance. Interestingly, Tre supplementation up-regulates stress response genes and induces the accumulation of various osmolytes including proline, glycine betaine and soluble sugars, which confer different kinds of stress tolerance. Alternatively, the development of transgenic plants with genes for Tre bio-synthesis leads to appreciable tolerance against different stresses. However, some transgenic plants over expressing Tre biosynthesis genes are adversely affected. This work aims to systematically review Tre's role as stress tolerance molecule and its crosstalk with other osmolytes under stress conditions, explaining mechanism of stress tolerance and pointing out areas for future research. It is evidenced that this compound owns a promising application as osmo-protectant in many crop conditions in the coming years. The present review is intended as means to enrich the awareness on Tre potential benefits, in order to help the scientists as well as the practitioners to improve crop behavior and ultimate production under stress conditions.

Keywords: Abiotic stresses, antioxidants, genetic engineering, osmoprotectants, signaling crosstalk, Trehalose

Introduction

Plants face different abiotic stresses (drought, salinity, heat, heavy metals, and cold) during their life cycle, with devastating impacts on their growth, physiology and cellular functioning (Sharma et al., 2019; Ghosh et al., 2021). The intensity of these abiotic stresses is continuously rising due to rapid climate change. It is well known that climate change is continuously increasing, which is a major reason for the growing intensity of abiotic stresses (Kaushal and Wani, 2016). Heat stress often leads to drought stress, and salinity stress is often associated with drought which negatively affects plant growth and development (Kaushal and Wani, 2016). The extent of the damage determined by these abiotic stresses is largely dependent on stress severity of stress and plant growth stage (Fahad et al., 2017). These abiotic stresses seriously disrupt plant cellular and development processes throughout their life cycle (Choudhary et al., 2019; Nadarajah et al., 2020 et al., 2020; Ghosh et al., 2021). More specifically, they reduce plant growth and development by negatively affecting photosynthesis, antioxidant defense, and hormonal signaling (Hassan et al., 2020; Hassan et al., 2021a; Ghosh et al., 2021). These abiotic stresses increase the production of reactive oxygen species (ROS) and cause membrane damage and lipid per-oxidation (Tanveer et al., 2019; Ghosh et al., 2021; Nagy-Réder et al., 2022), which results in 50-70% yield losses (Francini and Sebastiani, 2019) Therefore, reduction in crop productivity due to such stresses is posing a severe threat to global food security, and calls for strategies to reduce their impact on crop productivity in order to meet the demand of a rising population and ensure global food security.

Plants activate various cellular and molecular processes in response to stress conditions, resulting in improved growth and final productivity (Hassan et al., 2020; Hassan et al., 2021a; Rasheed et al., 2020a; Iqra et al., 2021). Plant cells allow the influx, synthesis, and sequestration of different solutes and their accumulation under stress conditions to support the cell turgidity, growth, development, and redox homeostasis (Hassan et al., 2019a; Chattha et al., 2021). The osmotic adjustment in plants is mediated by the synthesis and accumulation of osmolytes which protect the plant cellular machinery and improve the photosynthetic efficiency and antioxidant activity, resulting in sustained growth and production under stress conditions (Dey et al., 2021; Khan et al., 2021).The most common osmolytes accumulated in plants are glycine betaine (GB), proline and some specific sugars (mannitol, sorbitol, and trehalose) (Aamer et al., 2018; Hassan et al., 2019a; Dustgeer et al., 2021). The accumulation of these osmolytes in response to stressful conditions confers plant tolerance and improves plant growth and development (Ajnum et al., 2017; Imran et al., 2021). The cited sugars, in particular, play a crucial role in plant metabolic processes during their life cycle. There is an interplay between these sugars and hormonal signaling (ethylene, gibberellins, auxins and abscisic acid), which is critical for plant growth and development under stressful conditions (Ciereszko et al., 2018).

One of such essential sugar molecules is Trehalose. Trehalose (Tre) is an imperious disaccharide that was first discovered in a fungal (*Claviceps* spp.) mycelium of rye (Wiggers, 1832). Tre was found in higher quantities in different organisms such as bacteria and invertebrates, and lower quantities in higher plants. The spores of fungi and yeasts are considered enriched in Tre in a range of around 16-30% (Sols et al., 1971). Tre has no odor, white color, and is considered 45% sweeter than sucrose (Jain and Roy 2009). Tre has diverse plant functions, and works as potential osmo-protectant (Luo et al., 2021; Rohman et al., 2021). For example, Tre stabilizes dehydrated enzymes, proteins, and membranes and protects the biological systems from the devastating impacts of abiotic stresses (Luo et al., 2021; Rohman et al., 2021). Tre also works as an elicitor of genes involved in stress response and detoxification of reactive oxygen species (ROS) (Kosar et al., 2019). Nonetheless, the production of Tre in plants is not sufficient to alleviate the adverse impacts of different stresses. Thus, it is proposed that exogenously applied Tre contributes to internal Tre level, and this can be considered an alternative strategy for induction of stress tolerance in plants (Zulfiqar et al., 2021a). Exogenously applied Tre successfully alleviated the adverse impacts of different abiotic stresses (drought, heat, heavy metals and salinity) (Kosar et al., 2019; Rehman et al., 2022; Xie et al., 2022). This exogenously applied Tre plays a significant role as osmo-protectant to detoxify ROS and maintain the cellular osmotic balance by stabilizing the enzymes, proteins and membranes, and by ensuring better growth and development under stressful conditions (Mostofa et al., 2015a; Zulfiqar et al., 2021b).

Owing to the growing interest raised by substances capable of promoting plant stress tolerance, in this review we discuss the physiological and biochemical functions of Tre under various abiotic stresses. We also discuss the Tre mediated antioxidant defense system and biotechnological Tre synthesis, for improved stress tolerance. Also, Tre cross talk with different osmolytes is addressed to provide a more complete overview of Tre mediated stress tolerance. We believe that this review will provide researchers with new insights into the role of Tre in plants under abiotic stresses. Among other uses, this information will allow breeders to develop cultivars with improved Tre biosynthesis, which will surely improve the plant tolerance against different stresses.

Trehalose biosynthesis and metabolism in plants

The common pathway involved in Tre biosynthesis in prokaryotes and eukaryotes is the trehalose-6-phosphate phosphatase synthase (TPS) pathway, which comprises two steps (Paul et al., 2008). The first step involves the synthesis of the intermediate compound trehalose-6-phosphate (TTP) from glucose 6 phosphate and uridine in a reaction catalyzed by TPS. TTP is converted into Tre in the second step through dephosphorylation catalyzed by trehalose-6-phosphate phosphatase (TPP). Nonetheless, enzymes such as Ots-A and Ots-B in bacteria directly convert glucose-6-phosphate and UDP to Tre, which is a pathway similar to that found in plants and yeasts, although in these latter TPS1 and TPS2 catalyze the second step in place of TPS and TPP (Ponnu et al., 2011). Lastly, in plants, the TPS is converted into Tre as a final product with the help of trehalose-6-phosphate (Figure 1).

Endogenous Tre acts as a signaling molecule in plants linked with carbon allocation and dehydration stress (Schluepmann and Paul, 2011). Tre presence has been found in many angiosperm species as rice and tobacco (Gechev et al., 2014; Han et al., 2016). However, a very low Tre concentration (10 μg g^{-1}) was detected in rice and tobacco (Han et al., 2016). Scientists have recently focused on Tre metabolism in transgenic plants with special reference to stress tolerance (Schwarz and Van Dijck, 2017). A lower Tre concentration is not due to Tre's sole action, but also due to tight regulation of TPS and TPP gene expressions and enzymatic activities (Delorge et al., 2014). For instance, validamycin A addition to growing media increased Tre accumulation (Goddijn et al., 1997); however, up-regulation of Tre genes causes a marked increase in Tre biosynthesis in transgenic plants, which improves the stress tolerance (Delorge et al., 2014). The expression of *E. coli* and yeast-derived Tre genes in various plant species increase their tolerance against salinity, drought, and cold stresses (Iordachescu and Imai, 2008). For instance, higher expression of trehalose phosphate synthetase genes in rice induced the tolerance against salinity, cold and drought stress conditions, while in sugarcane the over expression of this gene increased drought tolerance (Li et al., 2011; Hu et al., 2020). Similarly, up-regulation of *AtTPS1 (Arabidopsis trehalose-6-P synthase)* in *Arabidopsis* induced a small increment in T6P and Tre, but TPP activity increased Tre level under low-temperature conditions (Suzuki et al., 2008). The exposure of *Arabidopsis* to heat stress (40 °C) increased Tre by two-folds within four hours, and Tre level increased to eight times when plants were exposed to cold stress after heat stress (Kaplan et al., 2004). The expression of Tre transgenes activates the biosynthetic Tre pathways in plants subjected to stress conditions. For instance, in cotton the TPS1 gene was expressed only in plant roots and leaves (Kosmas et al., 2006). Moreover, in maize plants the TPP gene was repressed in tassels, while TPS1 was over expressed in maize ears under water deficit conditions (Zhuang et al., 2007). Additionally, sometimes Tre degradation regulates the level of Tre in different plant tissues. For instance, in *Medicago truncatula* Tre gene (*MtTRE1*) was blocked under salinity stress; however, Tre concentration was substantially enhanced in crop nodules (López et al., 2008). In *Arabidopsis*, abiotic stress caused a significant increase in gene expression involved in Tre metabolism (Iordachescu and Imai, 2008). Thus, in light of the findings discussed so far it is concluded that Tre effectively induces stress tolerance in plants, and transgenic plants support the evidence that activated Tre metabolism triggers plant acclimation again different stresses.

Trehalose structural properties

Tre is a non-reducing sugar consisting of two sub-units of glucose linked by an alpha, alpha-1 and 1 glycosidic bond (Figure 1). Tre has special characteristics compared to other di-saccharide sugars because both reducing sub-units are involved in making the glycosidic (Jain and Roy 2009). Tre has appreciable resistance against hydrolysis and remains durable in the soluble form at higher temperatures with acidic pH (Onwe et al., 2021). Moreover, Tre possesses higher hydrophilicity due to internal hydrogen bonding (Paul and Paul, 2014). Due to these characteristics, Tre is a suitable molecular, membrane and protein preservative (López-Gómez and Lluch, 2012). Tre has excellent dehydrating and vitrification ability (Sakurai et al., 2008). Tre forms hydrogen bonding with surrounding macromolecules and membranes during dehydration by replacing water molecules (Olsson and Swenson, 2020). Moreover, under extreme water deficit conditions, Tre crystallizes into glassy appearance, a unique trait of this sugar (Cesaro et al., 2008; Einfalt et al., 2013). The glassy Tre formation preserves bio-molecules from dehydration and recovers their functional ability upon exposure to re-hydration (Fernandez et al., 2010). Tre is an inert sugar and has deficient chemical energy (1 kcal mol^{-1}) (Schwarz and Van Dijck, 2017). Conversely, sucrose has higher bond energy (27 kcal mol^{-1}) and does not break into the reducing mono-saccharides until it is exposed to Tre action or extreme hydrolytic conditions (López-Gómez and Lluch, 2012). These characteristics make Tre a good substance for inducing stress tolerance in plants.

Trehalose in stress tolerance

The critical role of Tre in plant adaptation and tolerance against several abiotic stresses is well documented. Tre can markedly improve plant tolerance against different stresses (Figure 2). Tre mediates diverse bio-chemical, physiological and molecular processes in plants to resume, adjust and maintain the tolerance against different abiotic stresses (Figure 2). Being a signaling molecule, Tre stimulates different processes and signaling pathways in response to stress. Currently, several efforts are being made to elucidate the role of various plants grown under different stress conditions. Here, we briefly discussed the Tre mediated plant tolerance against different abiotic stresses.

Trehalose induced salinity stress tolerance

Salinity stress is a major issue globally, which reduces plant growth and affects development through ionic toxicity and imposition of osmotic stress (Marriboina and Attipalli, 2020). However, Tre application is acknowledged to improve plant resistance to salinity in different ways in several species (Table 1). Tre supplementation was shown effective to stabilize proteins and membranes, and activate the antioxidant defense system (Abdallah et al., 2016; Rohman et al., 2019), which in turn reduced ion leakage and lipid peroxidation, resulting in substantial plant homeostasis under salt stress (Zeid, 2009). Tre protects the ionic pump by diverting the excessive amount of Na^+ from chloroplasts, protecting plant molecules from Na^+ damage and improving the plant photosynthetic efficiency and growth under salt stress (Garcia et al., 1997). Moreover, Tre supplementation maintains the potassium concentration, which improves stomata opening and carbon fixation under salt stress and increases carbon fixation and efficiency of PS-II, fostering increased assimilate production under salt stress (Garg et al., 2002; Rohman et al., 2019; Samadi et al., 2019).

Crop exposure to Tre induces the tolerance as shown by different reports. For example, Abdallah et al. (2020) exposed quinoa plants to different Tre concentrations (0, 2.5 and 5 mM) under varying levels of salt stress (0, 3000 and 6000 mg/L), which induced a marked increase in soluble sugars, proline, amino acids under both stressed and control plants. The increase in their accumulation upon Tre supplementation augmented photosynthetic pigments, antioxidant activities (ascorbic peroxidase, APX; catalase, CAT; peroxidase, POD; superoxide dismutase, SOD), which protected the plants from salt-induced oxidative stress and improved growth (Abdallah et al., 2020). Similarly, Sadak (2019) exposed wheat plants to different levels of salinity (0.23 and 6.25 dS/m) and Tre application (0, 10 and 50 mM). They noted that Tre supply improved the accumulation of soluble sugars and endogenous Tre, while reducing the lipoxygenase enzyme (LOX) activity and the accumulation of H_2O_2. The increase in endogenous Tre and osmoregulating compounds improve plant performance under salt stress (Chang et al., 2014; Sadak et al., 2019; Feng et al., 2019). Tre also acts as a signaling molecule that makes salt-affected plants actively increase free amino acids, reduce water losses, and control the leaf gas exchange and ionic flow in response to salinity stress to ensure better salt tolerance (Chang et al, 2014).

Tre supplementation maintains redox homeostasis and improves the antioxidant activities (APX, CAT, GPX, DHAR and MDHAR) which in turn maintain the membrane integrity of plants performing at optimum level under salt stress (Rohman et al., 2019). Tre supplementation also increased ABA accumulation by expression of genes linked with ABA synthesis under salt stress, which favors stomata closure and reduces the water loss to ensure better salt tolerance (Feng et al., 2019). In conclusion, Tre application can significantly offset the constraints to plant growth determined by salt stress, by improving photosynthetic and antioxidant activity, accumulation of ABA, K^+, compatible solutes, and soluble sugars, while concurrently restricting Na^+ accumulation.

Trehalose induced drought stress tolerance

Drought is a severe abiotic stress that has devastating impacts on plant growth and development (Hassan et al., 2017; Rasheed *et al.*, 2020a; Mubarik et al., 2021). Generally, drought stress induces osmotic stress and reduces plant growth and development, biomass production, root growth, turgor potential and photosynthetic rate (Hassan et al., 2017; Ahmad et al., 2022). However, many investigations demonstrate that Tre possesses an appreciable ability to counter the drought stress (Table 2) (Fatemeh et al., 2012). Tre supplementations significantly increased the growth of *Brassica* plants grown under drought stress conditions by substantially increasing the activities of antioxidant enzymes, assimilate production and the maintenance of membrane integrity and redox balance (Alam et al., 2014; Shafiq et al., 2015; Kosar *et al.*, 2020; Acosta-Pérez et al., 2020). Tre protects the cellular membrane and other plant biological structures from the damaging effects of water desiccation, owing to its change in physical state into glassy appearance, making it a prominent osmo-protectant playing a key role under drought stress (Acosta-Pérez et al., 2020). The increase in membrane protection and biological structures following Tre supply reduces lipid per-oxidation and leakage of osmolytes, and confers the drought tolerance in plants (Acosta-Pérez et al., 2020). Stomata movement changes substantially affect plant photosynthetic performance under drought stress (Kosar et al., 2018). Drought stress negatively affects photosynthetic rate (A), stomatal conductance (gs), transpiration rate (E), sub-stomatal CO_2 concentration (Ci) and WUE. However, Tre supplementation improved the aforementioned photosynthetic traits and improved the water use efficiency (WUE) in water deficit conditions (Ali and Ashraf, 2011; Kosar et al., 2018). Drought stress disrupts the stomata activities (Zulfiqar et al., 2021a), and Tre supplementation maintains K^+ influx and improves stomatal conductance and osmolyte accumulation, which improve plant water uptake capacity and plant WUE (Zulfiqar et al., 2020). Tre application also lowers the cell osmotic potential and increases water absorption from soil, leading to increased water uptake and WUE (Kaya et al., 2007; Parida et al., 2008).

Tre supplementation improved plant water content, the synthesis of photosynthetic pigments and reduces the MDA and H_2O_2 accumulation by increasing the antioxidant activities (APX, DHAR, GPX and CAT) (Alam et al., 2014; Khater et al., 2018). Nonetheless, Tre foliar spray (100 and 500 μM) improved plant growth, the number of leaves and branches/plant, and yield and its components in cowpea plants, by favoring the accumulation of soluble sugars, phenolic contents, and antioxidant substances (CAT, SOD, and POD) (Khater et al., 2018). Moreover, Tre possesses an excellent potential to improve the final product's quality. For instance, Kosar et al. (2021) noted that Tre supplementation (30 mM) significantly improved seed yield, oil and protein contents of sunflower by increasing the membrane stability and reducing the MDA and ROS accumulation (Kosar et al., 2021). The application of Tre (30 mM) significantly improved sweet basil growth and yield by increasing the accumulation of proline and glycine-betaine (Zulfiqar et al., 2021a). The increase in accumulation of osmolytes substantially increased growth and biomass production under water deficit conditions (Aldesuquy and Ghanem 2015; Zulfiqar et al., 2021). Tre supplementation also improved the accumulation of oleic and linolenic acid contents and increased antioxidant activity through the enhanced accumulation of tocopherols, flavonoids, and phenolics in maize oil (Ali et al., 2012). To summarize, Tre supply improves the accumulation of osmolytes and antioxidants, resulting in higher plant growth, and development under drought stress.

Trehalose induced heat stress tolerance

Heat stress (HS) is a serious abiotic stress which is causing serious yield losses across the globe (Hassan et al., 2021). The current global warming has increased the magnitude of HS, which induces excessive production of ROS damaging proteins, lipids, and DNA (Hassan et al., 2021a). Tre supplementation is found to play an imperious role in improving HS tolerance (Table 3). The increase in Tre content is correlated with an increase in HS tolerance (Mahmud et al., 2010; Cao et al., 2014). Tre application to wheat improved growth and biomass production under HS by reducing leaf water loss, increasing photosynthesis, protecting the photosynthetic apparatus from heat-and protecting the plants from oxidative damages (Luo et al., 2014). Heat stress causes membrane damage and lipid per-oxidation, in response to which Tre supply protects the membrane and reduces lipid per-oxidation and electrolyte leakage through increased antioxidant performance (Luo et al., 2010; Li et al., 2014; Liu et al., 2019a; Zhao et al., 2019). Moreover, Tre pre-treatment increased the efficiency of PS-II and D1 protein content in wheat seedlings, which leads to plant growth and development under drought stress (Luo et al., 2018a).

Tre supplementation also regulates the expression of glucose-6-phosphate dehydrogenase (g6pdh) and increases production of both nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione (GSH), to maintain optimum GSSG/GSH ratio and alleviate drought induces damages (Luo et al., 2020; Yan et al., 2021). Additionally, Tre increases the quantity of ferredoxin-NADPH oxidoreductase and up-regulates PS-I reaction center subunits, ATPase, FBPA, RuBisCo and the efficiency of PS-I and PS-II, resulting in an appreciable increase in plant growth and development under HS (Luo et al., 2018b). Conclusively, Tre protects the membranes photosynthetic apparatus, reduces lipid per-oxidation, ROS production and increases electron transport and subsequently plant growth under HS conditions. There is no information available about Tre's role in stomatal movements, nutrient uptake, and accumulation of different hormones (ABA, IAA, GA) and osmolytes under stress. Therefore, it would be fascinating to explore the role of Tre on stomata movements, nutrient uptake, hormone and osmolyte accumulation. This will open new insights into the role of Tre in mitigating deleterious impacts of heat stress in plants.

Trehalose induced cold stress tolerance

Cold stress is also a serious abiotic stress that considerably limits crop productivity across the globe. Generally, cold stress induces variations in cytoplasmatic viscosity and enzymatic activities, and causes chlorosis, necrosis and membrane damages (Ding et al., 2019). Tre can play a remarkable role in improving cold stress tolerance (Table 4), and it has been widely detected in cold tolerant crops, suggesting that Tre is involved in cold tolerance (Williams et al., 2015). Exogenous supply of Tre maintains membrane integrity and improves the efficiency of PS-II and quantum yield of PS-II, while reducing the electrolyte leakage which ensures better growth and subsequent yield under cold stress (Liu et al., 2021). Tre supply also elevates the endogenous Tre and NO, which stimulate the H_2O_2 levels, enabling plant stress responses. Tre mediated increase in Tre, NO and H_2O_2 contribute to Tre activity, improve the antioxidant activities and reduce the membrane lipid per-oxidant (Liu et al., 2021). The response to Tre priming (0.5, 1 and 2 mM) was studied on rice seedlings grown under cold stress conditions (15 °C). Tre priming increased plant growth and accumulation of proline, endogenous Tre, soluble sugars and activities of antioxidants (CAT, POD, SOD and APX) of rice and tomato plants (Fu et al., 2020; Liu et al., 2020), and accumulation of osmo-protectants resulting in improvement of growth performance under cold stress (Ding and Wang, 2018; Fu et al., 2020).

Tre application improved root growth and endogenous Tre levels, which promote increased water absorption and reduce water losses by decreasing the transpiration, therefore improving the RWC and subsequent plant growth under cold stress (Liu et al., 2014). Exogenous Tre supply decreased the floret degeneration and increased the fertility of florets, increasing grain production under cold stress (Liang et al., 2021). Tre supply also promoted nitrogen assimilation and reduced the ammonium accumulation in plant cells under cold stress. Additionally, exogenous Tre supplementation increased the endogenous spermidine, glutathione and ascorbic acid contents, and promoted the glutathione-ascorbic acid cycle, reducing ROS production and conferring cold tolerance in plants (Liang et al., 2021). To summarize, Tre supplementation improved the growth under cold stress conditions by reducing H_2O_2 accumulation while stimulating endogenous Tre, gene expression, polyamines accumulation, and antioxidant enzyme activities. Though, the role of Tre on stomata movements and nutrient uptake and subsequent transportation under cold stress is not explored. Therefore, future research is needed on these aspects to make an important osmo-protectant for inducing cold tolerance in plants.

Trehalose induced ultraviolet radiation stress tolerance

Ultraviolet (UV) radiations in the range of 280-320 nm are considered a severe stress agent that negatively affects plant health. UV radiations negatively impact plant growth, hormonal regulation and stress-induced antioxidants (Vanhaelewyn et al., 2016). The effect of Tre on the fungus *Aureobasidium subglaciale* was studied under UV light, gamma radiations, and heavy metals (Liu et al., 2017). The resistance in *Aureobasidium subglaciale* was linked with the stress protector Tre. The increase in the expression of trehalose-6-phosphate synthase gene TPS1 ensured a survival rate of 1% under gamma-radiation (20k Gy), 2% under UV dose (250 J/m^2) and 10% under lead stress (1500 mg/L), respectively (Liu et al., 2017). In another study, Jiang et al. (2018) investigated Tre impact on yeast grown under heat, salinity and UV stress. The over-expression of the TPS1 gene enhanced the Tre synthesis in the specific yeast, which significantly improved its tolerance against heat, salinity, and UV radiations by strengthening the antioxidant defense system (Jiang et al., 2018). Only a few studies are performed to determine the response of Tre application against the UV radiations stress. Therefore, a broad range of studies are needed to assess the impact of Tre on plant physiological and molecular responses under UV stress.

Trehalose induced heavy metal stress tolerance

Heavy metals are a severe concern to soil health, global food security and human health (Rasheed et al., 2020b; 2020c; 2020d). The intensity of heavy metal soil pollution has significantly increased due to anthropogenic activities. Heavy metals induce serious changes in growth, physiological, biochemical, and metabolic processes (Zain et al., 2021; Imran et al., 2021). Being a good antioxidant and signaling molecule, Tre possesses an excellent potential to mitigate the adverse impact of heavy metals. The effect of exogenously applied Tre was determined on rice seedlings grown under cadmium (Cd) stress. The application of Tre improved plant growth by decreasing Cd absorption and subsequent accumulation in plant parts. Additionally, Tre induced a significant increase in chlorophyll, calcium and magnesium concentrations under Cd stress, which also contributed towards improvement in seedling growth (Li et al., 2019). Tre application induced Cu and Cd tolerance by reducing Cu and Cd uptake and oxidative damages, by lowering MDA and ROS accumulation through increasing antioxidant activities (SOD, POD, GST, GST, GSH) and proline accumulation (Duman et al., 2011; Mostafa et al., 2015a; Rehman et al., 2022). Duman et al. (2011) also investigated the influence of Tre supplementation on aquatic plant growth under Cd stress. Tre supply (5 mM) appreciably improved proline accumulation and plant growth under Cd stress, reducing MDA and electrolyte leakage through enhanced membrane integrity (Mostafa et al., 2015). Tre (60 mM) appreciably improved seedling growth by reducing H_2O_2 and O^{2-} contents thanks to higher Tre induced antioxidant activities (CAT, POD and SOD), and maintenance of membrane integrity owing to increase in endogenous Tre synthesis (Wang et al., 2020).

In another investigation, Duman (2011) determined the response to Tre application (0.5, 1, 2 and 5 mM) in *Lemna gibba* plants growth under Pb stress (5, 10, and 25 µM): Pb accumulation in plants was significantly curbed by Tre application, with the strongest reduction being obtained at the highest Tre level (5 mM). Tre mediated heavy metal stress tolerance and antioxidant enzyme activities were induced by increased activity of trehalose-6-phosphate (Keunen et al., 2013; Martins et al., 2014). Tre also reduced the accumulation of the metal in plants by forming complexes with different metals present in the growing medium (Mostafa et al., 2015). The formation of metals and Tre complexes reduces the metals accumulation and subsequent transportation in plants, and ensures higher tolerance against heavy metal stresses (Mostafa et al., 2015). Thus, in light of the findings mentioned earlier, it is concluded that Tre alleviates the heavy metal-induced stress through reduced metal accumulation, enhanced accumulation of potential osmolytes and antioxidant activities. Nonetheless, mechanisms linked with Tre mediated heavy metal alleviation remain elusive, and more studies are direly needed to underpin them.

Trehalose induced nutrient deficiency tolerance

Plants need essential nutrients for unconstrained growth and development, and any nutrient deficiency can cause significant yield losses (Aslam et al., 2015; Chattha et al., 2017; Hassan et al., 2019b; Hassan et al., 2021). Nutrient deficiency is continuously soaring, which is causing a serious threat to food production and quality. Being an excellent osmolyte and signaling molecule, Tre can improve plant performance under nutrient deficiency. Tre coordinates carbon supply with growth, development and many physiological processes in the presence of carbon availability (Figueroa and Lunn, 2016). Tre pathway offers an opportunity to improve crop production; however, the primary challenge is to target such a robust regulatory mechanism for different crops under different conditions (Kretzschmar et al., 2015; Griffiths et al., 2016).

Nitrogen metabolism is closely integrated with carbon metabolism in all areas of plant functioning, including photosynthesis, where photo-respiratory nitrogen cycle results in significant turnover of total nitrogen and amino acids (Bernard and Habash, 2009). Genetic modification of TSP6 affects the photosynthetic machinery, output, and amino acid metabolism (Pellny et al., 2004; Zhang et al., 2009; Figueroa et al., 2016). Thus, modification of Tre pathway can improve the N metabolism and nitrogen use efficiency in plants. Moreover, exogenous Tre (8 mM) supplementation regulates nitrate and ammonia assimilation, and enhances nitrate reductase, glycolate oxidase and glutamine synthetase activities, while alleviating nitrogen deficiency in plants and improving plants growth and biomass production (Lin et al., 2017). Tre application appreciably improved the N assimilation and concentration and growth of plants by reversing the reduction in enzymes of nitrate and ammonium assimilation linked with N deficiency in plants (Lin et al., 2017). The low N contents also increased the endogenous Tre levels, which indicates that Tre pathway may regulate the N metabolic responses to N deficiency (Lin et al., 2017). Tre application alleviates nutrient deficiency and reduces MDA content, LOX activity and increased APX, DHAR, CAT, GPX, GR and MDHAR activities, which contributes to significant increase in growth under nutrient deficient conditions (Rohman et al., 2019). Though, these are only information available in the literature describing the role of Tre under nutrient deficiency. Thus, it is direly needed to perform more studies to explore the role of Tre in plant physiological, biochemical, and molecular responses under nutrient deficiency. Targeting the Tre pathways could be an imperative way to improve the plant growth under nutrient deficit conditions, and potentially improve nutrient use efficiency in field crops. As Tre application is not practicable, targeting Tre path using genetic practices could be a desirable choice to improve nutrient use efficiency in field crops.

Role of trehalose-mediated antioxidant defense system

Plants stage a wide range of physiological and biochemical adaptations to cope with abiotic stresses. Different abiotic stresses induce ROS production (Sachdev et al., 2021) which causes damage to macromolecules and biological membranes (Chattha et al., 2021). Therefore, plants produce enzymatic and non-enzymatic antioxidants to protect themselves from the damaging effects of abiotic stresses (Rajput et al., 2021). Being a potential osmolyte, Tre can not only improve plant growth but also upgrade the antioxidant deference system under stress conditions (Table 6). Because of special characteristics like hydrogen boding, glassy appearance and stronger hydrophilicity, Tre plays an appreciable role in increasing the antioxidant activities under stress conditions (Abdallah et al., 2016). Further sources report that Tre considerably improved proline accumulation under drought stress and shielded the biological molecules by activating the antioxidant defense system (Rezvani and Shariati 2009; Shahbaz et al., 2017).

It was noticed that Tre supply (50 mM) neutralized the adverse impacts of HS by reducing ROS accumulation and protecting the CAT, SOD and POD enzymes under salt stress, and ameliorated the negative impacts of salt stress (Luo et al., 2008; Dolatabadian and Jouneghani, 2009; Luo et al. 2010; Nounjan et al., 2012; Abdallah et al., 2016). Tre supply also increased the endogenous Tre level, GB and proline accumulation, which favored the increase in CAT (16%), POD (12%) and SOD (26%) activities to induce drought tolerance in sweet basil (Zulfiqar et al., 2021a). Tre induced the reduction in lipid peroxidation, H_2O_2 accumulation and LOX activity through enhanced activities of APX (40%), CAT (52%), POD (32%) and SOD (46%) under normal and water-stressed conditions (Ibrahim and Abdellatif, 2016; Sadak et al., 2019; Kosar et al., 2021). The application of Tre caused a significant increase in APX (34%), CAT (22%), GH (30%), POD (29%) and SOD (30%) activities, which reduced the H_2O_2 and O^{2-} accumulation under $NaHCO_3$ induced stress, and increased the tolerance of *Iris dichotoma* (Liu et al., 2009). In conclusion, the cited sources support the finding that Tre application effectively improved plant tolerance against different stresses by regulating the activities of antioxidant defense system. However, more studies are needed to determine how Tre induces antioxidant activities under stress conditions. More studies are also required to explore the signaling cross-talk between Tre and the antioxidant system under stressful situations.

Trehalose as a potential osomolyte

Different compatible solutes are produced in plants that protect the biological structure and major molecules from exposure to different abiotic stresses (López-Gómez and Lluch, 2012). The deleterious impacts of different abiotic stresses induce the accumulation of different osmolytes including Tre that protect the cellular membranes and biological structure from the damaging effects of drought, salinity and HS (Lei et al., 2019; Zulfiqar et al., 2021b). For instance, the presence of Tre in roots of *Phaseolus vulgaris* made them resistant against drought stress by increasing the osmotic potential (Farías-Rodriguez et al., 1998). *Arabidopsis* seedlings supplemented with Tre were elicited their responses, and more carbon was reserved owing to better starch accumulation in cotyledons from the fixed carbon (Wingler et al. 2002). Salt stress induces reduction in root meristem and cell size, in response to which, Tre helps to maintain root growth and counter the negative impacts of salinity stress (Ma et al., 2013).

Zeid (2009) noted that foliar-applied Tre enhanced chlorophyll content and the Hill reaction. Likewise, exogenous Tre applied to rice increased root integrity and regulated ionic balance and gene expression under salt stress (Fernandez et al., 2010). Moreover, in the radish crop exogenous Tre played an appreciable role as an osmo-protectant in plant physiology (Shafiq et al., 2015). Likewise, Abdallah et al. (2020) noted that Tre improved the accumulation of soluble sugars and carotenoids, and scavenged the ROS in rice seedlings grown under saline conditions. Additionally, in *Arabidopsis* Tre supplementation maintained the ionic hemostasis and increased the soluble sugars and antioxidant activities that, together, nullified the adverse impacts of salt stress (Yang et al., 2014). Tre also plays a significant role in embryo formation and flowering, and regulates carbon metabolism; moreover, interaction between plants and microorganisms also depends on the presence of Tre (Iturriaga et al., 2009). Tre (25 mM) application significantly improved the proline and GB accumulation, which improved the chlorophyll synthesis, antioxidant activities, carbohydrate contents, and endogenous Tre contents which in turn improved the salt tolerance in tomato plants (Xie et al., 2022). Similarly, in mungbean plants exogenous Tre (30 mM) significantly improved the free amino acids and total soluble protein contents, which induced a significant increase in growth and yield and mitigated the adverse effects of Cd stress (Rehman et al., 2022). Therefore, the role of Tre in plant metabolic processes may be the preservation. However, it is not fully elucidated to what extent Tre can protect the plant molecules and biological structure from different stresses.

Interaction and crosstalk of trehalose with other osmolytes

The balance amid the plant defense mechanism, growth and development is a complicated process. Therefore, studying osmolyte talks is indispensable for recognizing their role in different stress conditions. Studies have reported that Tre significantly regulates plant growth and development under unfavorable conditions. The exogenous Tre supply significantly increased GB and proline concentration by a respective 18% and 38% under drought conditions (Zulfiqar et al., 2021a). Another study noted a positive association between Tre supply and proline under stress conditions (Abdullah et al., 2020).

Moreover, Ibrahim and Abdellatif (2016) noted that foliar spray of Tre (5 mM) induced a significant increase in proline, soluble sugars (glucose, fructose, sucrose) and free amino acids, which provided protection against salinity. In another study, it was noted that Tre application significantly increased proline concentration in plants grown under salt stress conditions (Abdallah et al., 2020). Additionally, *Arabidopsis* treated with Tre under saline conditions showed a significant increase in soluble sugars. Similarly, a group of researchers suggested that Tre acts as a signaling molecule during salinity stress and improves the accumulation of soluble sugars and free amino acids to control water loss and maintain the ionic balance and leaf gas exchange (Chang et al., 2014). The application of Tre also induces a significant increase in endogenous Tre content, which ensures stress tolerance in plants (Ma et al., 2013). Tre supplementation also improves the accumulation of phenols and flavonoid contents which substantially increased the drought tolerance in plants (Aldesuquy and Ghanem, 2015; Sadak, 2016; Dawood, 2017). The increase in phenolics and flavonoid accumulation following Tre supplementation can be attributed to the role of Tre as molecule which triggers the plants to activate non-enzymatic antioxidants for ROS scavenging (Ibrahim and Abdellatif, 2016). In another study, it was noted that exogenous Tre works as inducer of H_2O_2 and NO that regulate genes expression and promote plant response to cold stress. Tre could also increase the endogenous H_2O_2 and NO levels, which trigger plant responses against abiotic stresses. Moreover, H_2O_2 and NO participate in the roles of Tre, and NO might be located downstream of H_2O_2 to improve the antioxidant activities and protect the plants from damaging effects of cold stress (Liu et al., 2021). Tre also up-regulates the expression of salicylic acid (SA)-dependent genes, which in turn increase the accumulation of SA. Moreover, Tre also increases the accumulation of jasmonic acid which in turn improves the drought tolerance in plants (MacIntyre et al., 2022). In conclusion, Tre supply appreciably reduces the negative impact of abiotic stresses. However, there is limited information about Tre cross talk with different osmolytes and soluble sugars. Moreover, Tre signaling and functioning in crosstalk with other osmolytes must be revealed at cell and tissue levels, as there is no information available on this aspect in the literature. Future research must also aim to better dis-entangle functions and control of Tre and its crosstalk with other sugars and osmolytes.

Trehalose as a biotechnological tool to enhance abiotic stress tolerance

The classical biotechnological approaches are being used globally to improve plant tolerance against abiotic stresses by strengthening the endogenous defense mechanisms. The hormonal cross-talk and accumulation of various osmolytes and soluble sugars affect plant defense responses, growth, development and abiotic stress tolerance. Due to promising Tre characteristics, efforts are made across the globe to develop transgenic plants over-accumulating Tre for conferring stress tolerance. The introduction of various yeast and bacterial-derived genes in many plants including rice, potato, tomato and *Arabidopsis* has made them stress tolerant (Karim et al., 2007; Iturriaga et al., 2009). The manipulation of Tre in micro-organisms can be a promising technique to enhance abiotic stress tolerance compared to introducing the related genes into plants. For instance, microbes as rhizobia produce large amounts of Tre (McIntyre et al., 2007; Sugawara et al., 2010; Sharma et al., 2020) and are stress responsive; thus, constant Tre production by plants would be unnecessary (Sharma et al., 2020).

The over-expression of Tre genes in transgenic plants made them more tolerant (Sah et al., 2016). For instance, transferring two Tre biosynthesis (otsA and otsB) genes from *E. coli* into rice has made this plant more tolerant (Garg et al., 2002). Plants with Tre biosynthesis genes had 3-10 times more Tre under stressful environments than normal conditions (Garg et al., 2002). The transgenic tobacco plants with TP genes from *Pleurotus sajor-caju* resulted in a substantial increase in stress tolerance capacity of tobacco plants (Han et al., 2005). Similarly, expression of OsTPS1 gene in rice induced an appreciable tolerance against stressful environment (Li et al., 2011). Moreover, yeast based TPS1 gene expression in the tobacco crop made it tolerant against the oxidative stress (Cortina and Culiáñez-Macià, 2005). Additionally, AtTPS1 genes transferred into tobacco plants from *Arabidopsis* made these plants more tolerant against stress conditions (Almeida et al., 2007). The engineered *Arabidopsis*, tobacco and melon plants with yeast orientated TPS and AtTPS1 genes showed strong tolerance against drought stress and some phenotypical changes (Serrano Avonce et al., 2004; Miranda et al., 2007). Likewise, over-expression of TPSP gene (a chimeric gene generated by fusing TPS and TPP enzymes) induced significant increase in endogenous Tre in transgenic rice and improved its stress resistance (Redillas et al., 2012). In transgenic rice, over-expression of OsTPP1 activated a series of stress related genes which induced a significant stress tolerance (Ge et al., 2008).

The aim of Tre modern biotechnological approaches is to produce tolerant transgenic plants and Tre at lower cost (Zheng et al., 2015), which can be used for pharmaceutical and other purposes. Tre engineering can help to find new advancements in plant metabolic processes. Plants interactions with bacteria, insects, and pathogens show that Tre acts as promising signaling molecule. Trehalose-6-phosphate works as a signaling molecule to maintain the sucrose level and sugar metabolism (John et al., 2017). T6P at lower concentration inhibits the SnRK1 (SNF1/AMPK group of protein kinases) and works as signaling agent involved in metabolism associated with carbon supply (Schluepmann and Paul, 2009). In *Arabidopsis* over-expression of *AtTPPF* genes also increased the endogenous Tre which conferred the drought tolerance, regulated the Tre levels and improved the plant performance under drought stress (Lin et al., 2019). Likewise, in transgenic *Arabidopsis* plants different genes (*ScTPS1* and *ScTPS2*) over-expression increased the Tre biosynthesis which in turn increased the drought tolerance by increasing antioxidant activities (Lin et al., 2020). Moreover, Jiang et al (2019) found that OsTPP3 over-expressing plants depicted a substantial increase in Tre synthesis, which improved soybean growth and photosynthetic performance by protecting the photosynthetic system through improved antioxidant activities. In another study, it was noted that increase in expression of Tre-biosynthesis genes (TPS4, TPS8, and TPS9) improves antioxidant activities, osmotic balance and participates in Tre metabolism and signaling network, which in turn improve the cold tolerance, antioxidant and osmotic balance, but it also significantly participates in Tre metabolism and signaling network to improve the CS tolerance in rapeseed (Raza et al., 2022). Likewise, Yang et al., (2022) also noted that Tre application improved the activity of enzymes involved in Tre metabolic pathway and expression of Tre genes (SlTPS1, SlTPS5, SlTPS7, SlTPPJ, SlTPPH, and SlTRE), which in turn improved salt tolerance by increasing antioxidant activities and accumulation of proline and GB. In maize plants it was reported that increase in TPS gene expression substantially improved the growth and drought tolerance (Lowantha and Hannok, 2022). Thus, the engineering of Tre biosynthesis in plants can be a promising option to improve the stress tolerance. Moreover, a genetic cascade of Tre can be thoroughly investigated by comparing Tre enriched vs. deficient plants subjected to different stress and non-stress conditions.

Negative effects of over-expressing trehalose biosynthetic genes on plants

Plant breeding and genetic engineering techniques got the appreciable results of improving the synthesis of endogenous Tre for conferring stress tolerance in plants. Many authors noted that an increase in Tre biosynthetic genes expression increased the synthesis of endogenous Tre and made the plants tolerant against different stress conditions (Sah et al., 2016; Liang et al., 2019; Lin et al., 2019; Lin et al., 2020). Nonetheless, some authors also noted negative results for over-expression of Tre genes in some plants. For instance, over-expression of TPS and TPP genes from yeast and *E. coli* in tobacco produced undesirable results, including alteried metabolism and stunted growth (Pilon et al., 1997; Smith et al., 1998). Likewise, increased over-expression of Tre gene (TPS1) in transgenic plants resulted in stunted growth and lower biomass production (30%), leaf area, stomata number, and CO_2 fixation under normal conditions (Karim et al., 2007; Stiller et al., 2008, Cominelli and Tonelli, 2014). Moreover, Goddjin et al. (1997) noted that in transgenic tomato and tobacco overexpression of Tre synthesis genes (TPS, TPP, otsA and otsB) also caused stunted growth and changed the leaf phenotypic appearance.

Additionally, according to Wingler and Paul (2013), overexpression of T6P genes in transgenic plants also induced negative impacts including severe leaf shading. The reasons for this growth inhibition are not clearly understood. The metabolic intermediate (T6P) similar to other plants' sugar phosphates is considered to have negative impacts on plant growth and development. This impact could be produced owing to T6P over-production in transgenic plant cells lacking the corresponding higher quantity of exogenous phosphatase needed for carrying the conversion of T6P into Tre. However, the negative effects of Tre over-expressing genes can be reduced by changing the Tre biosynthesis pathway; turning it on only when the plants face any stress condition.

Concluding remarks and future perspectives

Trehalose has gained considerable attention in recent times owing to its appreciable characteristics and ability to work as signaling molecule against diverse abiotic stresses. Trehalose determines changes in plant physiological, biochemical and molecular mechanisms by regulating the expression of genes promoting tolerance against different stresses. Trehalose application under different stresses reduces ROS production by increasing the activities of antioxidant enzymes and the accumulation of soluble sugars and other compatible solutes. Generally, plants accumulate a meager quantity of Trehalose, which is considered to be insufficient for maintaining growth and development. Therefore, efforts are underway to engineer the plants with appreciable ability to accumulate sufficient levels of Trehalose to alleviate the adverse impacts of abiotic stresses. Trehalose biosynthesis genes from microorganisms can be inserted in plants to make them tolerant against stress conditions. In this respect, the search for more convenient sources of Trehalose genes instead of microorganisms (bacteria and yeasts), to be inserted into plant genomes, is very active. Because the use of modern biotechnological approaches for improving Trehalose levels in plants is rather expensive, researchers recommend the exogenous use of Trehalose to improve the stress tolerance. The exogenous application of Trehalose is considered cost-effective; however, it is still unclear whether the effects of exogenously applied Trehalose would remain long lasting until terminal plant growth.

Globally, efforts have been made to clarify Trehalose role in different physiological processes, although its role in plant protection is not sufficiently explored. Thus, extensive research is needed to explore the Trehalose role in plant metabolism from the cell to the whole plant level. The information on Trehalose induced regulation of plant metabolism and morphology would help to determine the amount of Trehalose application. Likewise, anatomical changes taking place as a result of Trehalose application need to be explored. The effects of Trehalose application on final seed quality, composition and antioxidant activities must also be explored. The role of Trehalose in signaling pathways must also be explored to make it a promising osmo-protectant. Studies have shown that there is crosstalk between Trehalose and other osmolytes (proline, glycin-betaine, and sugars). However, the number of such studies is still limited regarding the need to underpin the Trehalose role and its crosstalk with osmolytes and sugars under different stresses. Furthermore, studies are also needed to explore if Trehalose under a combination of different stresses would still deliver promising results. Additionally, Trehalose signaling mechanisms and functions in different signal crosstalks at cell, tissue and organ levels are not fully explained. The effects of Trehalose under UV radiation stress and nutrient deficiency is not fully elucidated; thus, studies are direly needed to investigate the mechanisms lying behind alleviation of these stresses. The effect of Trehalose supply on heat shock and late embryogenesis proteins is still untouched. Further research is needed to acknowledge Trehalose's impact on expression of heat shock proteins under different stresses, single and combined. More studies are also needed to explore the role and mechanisms of Tre in mediating the water logging stress. Similarly, Trehalose role under heavy metal stresses is also not fully cleared. So, Trehalose's role in alleviating heavy metals' adverse effects must be fully explored to make it a promising protectant against heavy metal stress.

There is also missing information related to Trehalose crosstalk with different hormones under stress conditions. Therefore, it would be useful to unfold and discover Trehalose role in increasing the endogenous hormones and its crosstalk with hormones to counter the effects of different abiotic stresses. Recent improvement in genomics, transcriptomic, proteomics, and metabolomics has provided the clues to complex gene protein interactions and linked networks. These techniques would better understand hormonal regulatory networkings and their crosstalk under different abiotic stresses. Thus, it is direly needed to fully elucidate the potential of modern techniques for identifying Trehalose related proteins, genes, and metabolites for stress-tolerant plants. The discovery of Trehalose mediated regulatory and metabolic pathways can provide new insights to understand the signaling network under different stress conditions. Moreover, genetically engineered Trehalose mediated signaling and metabolic pathways would open new vision into existing knowledge to elucidate Trehalose mediated stress tolerance mechanisms. CRISPR has emerged as an excellent gene editing tool and this technology can assist to edit the genes responsible for Tre synthesis. The Tre biosynthesis in plants can be increased the CRISPR technology which will surely increase the abiotic stress tolerance in plants.

List of abbreviations

ABA: abscisic acid, APX: ascorbic peroxidase, CAT: catalase, DHAR: dehydroascorbate reductase, GA: gibberellic acid, GB: glycine betaine, GHS: glutathione, GPX: glutathione peroxidase, HS: heat stress, H_2O_2: hydrogen peroxide, IAA: Indole-3-acetic acid, LOX: lipoxygenase enzyme, MDA: malondialdehyde, MDHAR: monodehydroascorbate reductase, NO: nitric oxide, POD: peroxidase, ROS: reactive oxygen species, RWC: relative water contents, PS: photo-system, SOD: superoxide dismutase, T6P: trehalose-6-phosphate phosphatase synthase, TPP: trehalose-6-phosphate phosphatase, Tre: trehalose, UV: ultraviolet, WUE: water use efficiency.

Author contribution

Conceptualization: MUH, MN, ANS, Writing original draft: MUH, MN, ANS and LB, writing review and editing: MS, MH, MB, SP, SA, YSM, AES and SHQ. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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