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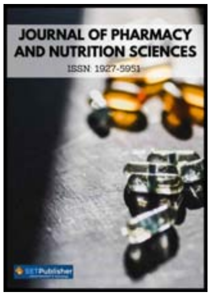

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# Glycine Betaine: A Potential Secondary Metabolite against Abiotic Stresses

Amantika Singh, Pooja Singh and Krishna Kumar Choudhary*

*Department of Botany, MMV, Banaras Hindu University, Varanasi-221005, India*

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**Abstract:**

Abiotic stresses like temperature, water, salinity, ultraviolet (UV) radiations, heavy metals, etc., affect plants' growth and yield. Despite these constraints, plants produce a variety of metabolites to maintain their survival. Primary metabolites, produced through crucial metabolic processes, are essential for plants survival. Additionally, secondary metabolites (SMs) are synthesized from primary metabolites and are mainly used as a defensive mechanism and a means of interacting with unfavorable environmental conditions. In addition to their defensive function in plants, SMs are significant in the pharmaceutical industry. Glycine betaine (GB) is a quaternary ammonium compound that belongs to a class of SMs, present in plants, animals, and microbes. It functions as a compatible solute and reflects potential bioactivity against various abiotic stresses like salinity, water, heat, heavy metals, UV radiations, etc. Due to high solubility and low viscosity, its accumulation is commonly observed in chloroplasts and plastids. The accumulation level generally depends on plant species, growth stage, exposure duration, and stress's nature. GB reduces oxidative stress and prevents the damaging of photosystems and other biomolecules under stressful conditions. It is important for maintaining the water potential and osmotic pressure of cells and hence functions as a potent osmolyte under salinity stress. Excessive production of ROS during temperature stress is responsible for damage to oxygen-evolving complexes, electron transport chains, and photosystems. In order to protect plants from these damages, GB activates the genes responsible for synthesizing heat shock proteins, glycoproteins, and antioxidants via various signaling pathways. GB alleviates the effect of water stress by maintaining the function of rubisco and calcium ion ATPase activity via crosstalk with Abscisic acid (ABA) and ethylene. GB supports the proper functioning of the ascorbate-glutathione cycle, superoxide dismutase, catalase, peroxidase, and ascorbate peroxidase (antioxidative enzymes) to overcome various stresses. Phytohormones like salicylic acid (SA), jasmonic acid (JA), ABA, ethylene, and polyamines (PA$_S$) coordinate well with GB via different signaling pathways to ensure plant protection under various abiotic stresses. The potential bioactivity of GB against various abiotic stresses in plants has been summarized in this review.

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*Corresponding Author
Mob: +91-7860953153:
E-mail: kkc@bhu.ac.in

## INTRODUCTION

A significant increase in the intensity, frequency, and duration of various abiotic stresses on this earth's surface has been observed in the past few decades due to the industrial revolution and global climate change. Abiotic stresses play a significant role in driving and shaping any ecosystem by affecting vital ecological processes. Plants are affected primarily due to their sessile nature. The overall manifestation of abiotic stresses is osmotic imbalance and excessive accumulation of ROS. ROS enhances the degradation of lipid membranes, photosynthetic pigments, plant proteins, nucleic acids, and various cell organelles, along with their functions, leading to programmed cell death, as depicted in Figure **2** [1].

Soil salinization is one of the significant abiotic stresses responsible for the degradation of around a 1125million hectares of land globally [2]. India occupies 6.727 million hectares of salt-affected land, which is 2.1% of its geographical region [3]. Approximately about 25% area of the Indo-Gangetic basin receives saline water [4], 44% area is covered under 12 states, and one union territory is salinity affected [5], out of which Gujarat, Uttar Pradesh, and Maharashtra are the major contributors [6]. A global economic loss of USD 27.3 billion annually has been observed due to salinity [7]. Salinity is responsible for the deterioration of soil fertility and quality, along with osmotic and ionic imbalance. The generation of ROS under salinity stress ultimately causes a reduction in the growth and yield of plants [8]. Plants utilize antioxidative defense mechanisms to counter excessive ROS [9] and maintain osmotic balance via potent osmolytes accumulation such as GB to overcome the negative impact of salinity and other stresses, as shown in Figure **1** [10, 11, 12].

The land is the primary source of (more than 95%) food produced [13]; flood and drought are two significant aspects of water stress affecting productivity. According to the National Disaster Management Authority (Government of India), more than 40-million-hectare land is prone to flood, and about 75-million hectare land is affected by seasonal floods yearly. The condition is similar to drought stress. Since the year 2000, the frequency and severity of drought have been increased up to 29 %, affecting 55 million people yearly [13]. As per the prediction, about three-quarters of the world's population may be affected due to drought by the end of 2050 [13]. Thus, water stress is imposing a serious threat to plant productivity and global food security. Water stress causes the overproduction of ROS like hydrogen peroxides, superoxide radicals, and hydroxyl radicals which causes lipids peroxidation to hamper plants' growth and leads to programmed cell death [14]. Plants tend to synthesize several osmolytes like GB (Figure **1**), proline, and sugars and stimulate antioxidant defense systems to maintain their sustainability under water stress [15].

On the other hand, an increase in average earth temperature has been observed due to global climate

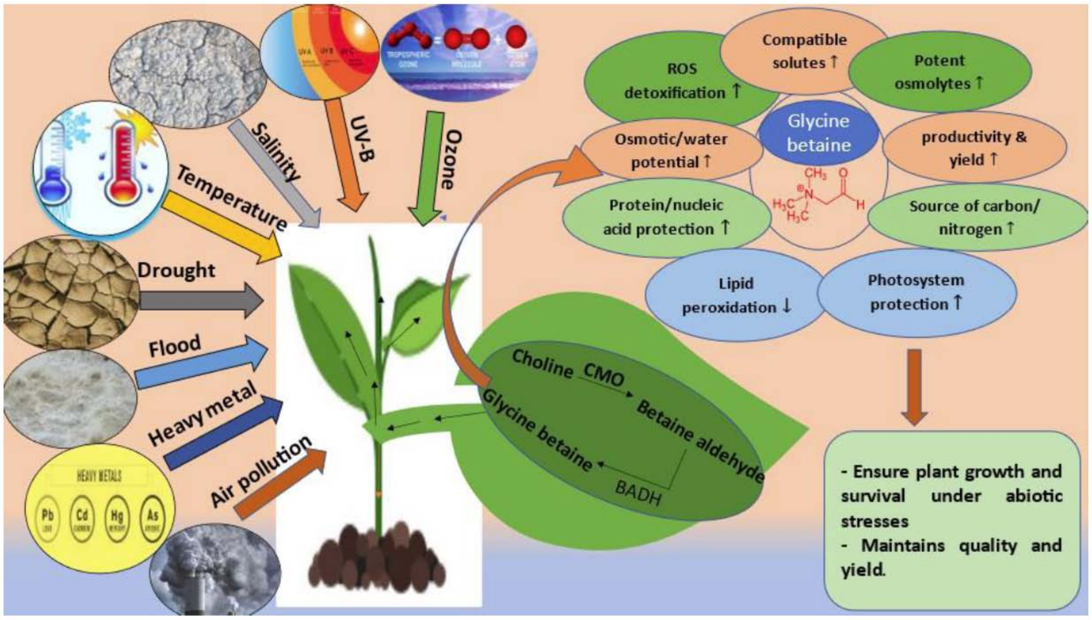

**Figure 1:** Role of glycine betaine under various abiotic stresses. CMO (choline monooxygenase); BADH (betaine-aldehyde dehydrogenase); ↑ (increase); ↓ (decrease).

change. The year 2021 was the sixth warmest year, as it was 0.84°C higher than the average of the 20th century [16]. As per the current rate of $CO_2$ emissions and other greenhouse gases, it is predicted that the earth's temperature will rise by 10.2°C by the end of this century [17]. Temperature stress can be classified as chilling stress (0-15°C) and freezing stress (≤0°C), depending upon the exposure of plants. This interferes with the normal metabolism of plants and causes oxidative stress, affecting plants' productivity and yield [18].

Besides this, the industrial revolution played a significant role in increasing heavy metals in the environment. In order to lessen the detrimental effects of heavy metals, GB accumulation in plants is enhanced, as shown in Figure **1**. These heavy metals enhanced ROS's overproduction, which hampers plant growth and productivity [19]. GB proved beneficial in terms of increased chlorophyll content, $F_V/F_{M,}$ and antioxidative enzymes in cadmium-stressed maize seedlings [20]. GB enhances the antioxidant capacity, and nutrient uptake and reduces the uptake of heavy metals, which improves the growth and productivity of plants [21]. In chromium-stressed chickpeas, GB was responsible for increased $H^+$ ATPase activity, improved root growth, reduced oxidative stress, and improved plasma membrane integrity [22]. Exogenous GB enhances biomass, mineral nutrients, pigments, antioxidants, and osmolytes in the lead (Pb) stressed *Brassica Chinensis* L. [23]. Similarly, accumulation of low molecular weight osmolytes like GB was observed under increased UV-B radiation as shown in Figure **1** [24]. Pretreatment of 50 mM GB via seed soaking (24 hours) in fenugreek reflected increased total soluble sugar and the accumulation of potential SMs under UV exposure [25]. The beneficial impact of GB was also observed for rice against elevated UV-B radiation [26]. *Florencia campestris* and *Flourensia oolepis* reflected the higher accumulation of GB after UV-B exposure [27]. Low molecular weight, highly soluble, and nontoxic compatible organic solutes are synthesized by plants as a response to various abiotic stresses [28]. These compatible solutes are amino sugars (glycine, alanine, proline, glutamine), sugars (sucrose, trehalose, maltose, fructose), sugar alcohols (Mannitol, sorbitol, inositol, pinitol), quaternary ammonium compounds (β-alanine, betaine, proline) and tertiary sulfonium compound (dimethyl sulfoniopropionate).

GB is a unique secondary metabolite (SM) [29, 30], a quaternary ammonium compound that is N, N, N-trimethyl glycine with the chemical formula ($C_5H_{11}NO_2$). It is a zwitterionic, dipolar, and electrically neutral compound at physiological pH [31]. Precursor of GB is choline and glycine [32), and it is synthesized via the choline monooxygenase pathway (CMO) (Figure **1**) / choline dehydrogenase (CDH)/ choline oxidase (COD) pathway [33] in plants and bacteria. It is synthesized in the stroma region of chloroplasts and other plastids of mature and older tissues [34] and transported to younger tissues through phloem via secondary active transports ($H^+$symporter). Cytosolic biosynthesis of GB is related to the non-stress condition [35], whereas chloroplastic biosynthesis is related to abiotic stress tolerance [36, 37]. In contradictory some reports are also suggesting no influence of GB under stressful conditions in *Oryza sativa* L. [38, 39], *Arabidopsis* [35], *Nicotiana tabacum* L. [35], and *Solanum Lycopersicum* L. [35]. GB contributes to plant defense against various abiotic stress [30, 40, 41], balances the cell osmotic/water potential [42], and helps to reduce lipid peroxidation along with protection to photosystems, proteins, nucleic acids via ROS detoxification [42]. It also serves as a function of carbon and nitrogen source [42] and ensures plants' growth, yield, and survival under various abiotic stresses, as shown in Figure **1**.

## Functions of Glycine Betaine as a Secondary Metabolite

Secondary metabolites (SMs) are bioactive substances produced by plants and are vital for plant survival under biotic and abiotic stresses. They also serve as barriers against herbivore deterrents, pathogen invasions, and oxidative stress mitigators. Environmental factors such as light, temperature, water, and soil quality significantly impact the accumulation of SMs [43]. SMs also play an important role as multifunctional metabolites frequently used by plants to communicate with their environment and defend themselves against various abiotic challenges like UV radiation, temperature, drought, and salinity [44, 45].

Glycine betaine functions as SMs [29, 30], which protects against abiotic stresses by acting as a powerful osmolyte [46]. It also serves as a compatible solute and shields plants from various abiotic challenges, including drought, salinity, temperature, and heavy metals [47, 48]. The plants' tolerance to various abiotic stress is increased by exogenous glycine betaine supplementation and transgene-mediated insertion of the glycine betaine biosynthesis gene in GB nonaccumulators to improve stress tolerance capacity [49, 50]. In GB-deficient species of higher plants, genetic engineering has made it possible to introduce genes from its biosynthesis pathway, reflecting the significance of GB in stress protection [46, 51, 48].

Plants have been transformed using genes that direct choline-to-GB processes; so far, they have been engineered to express (COD, CDH, or CMO). The first instance of synthetic GB production in plants was shown after *Arabidopsis* chloroplasts overexpressed the COD gene from *Arthrobacter globiformis* [52]. The enzyme was engineered with a chloroplast-targeting signal due to its bacterial origin, and as a result, GB accumulated in the chloroplasts at a concentration of 50 and 100 mM [53]. However, the production of GB increased three to five times more when COD was made to stay in the cytosol as opposed to the chloroplasts. This discrepancy may be due to a more significant concentration of the substrate choline in the cytosol (where choline synthesis occurs) than in chloroplasts [54, 55].

Additionally, transgenic rice plants were developed to produce CDH and COD that accumulate GB at comparable rates [56]. Transgenic maize lines showed a significantly enhanced accumulation of GB [57]. The model plants *Arabidopsis thaliana*, *Eucalyptus globulus, Japanese persimmon* (Diospyros kaki), *Brassica campestris* L. spp., *Solanum tuberosum*, and *Lycopersicon esculentum* were also overexpressed with the *Arthrobacter* spp. codA gene to produce tolerance against salinity, drought, chilling, and low relative humidity [11]. GB provides tolerance against chilling stress mediated through a G-protein called RabAc4, which is involved in membrane trafficking [48].

The stabilization of proteins and enzymes' natural structures, osmotic control, membrane integrity, reinforcement of photosynthesis, and detoxification of ROS generated during stresses are all components of GB-mediated abiotic stress tolerance mechanisms [58]. The GB functions *in vivo* as a chaperone protein; this shows that it can stabilize transcriptional and translational pathways to express genes in stressful conditions effectively. Studies conducted *in vitro* show that GB lacks antioxidant activity on its own [59, 60]. Rather than its direct action, GB indirectly activates the ROS defense system. Therefore, GB is a potential secondary metabolite to give plants a tolerance to abiotic stresses.

## Salinity Stress and Glycine Betaine

Salinity stress negatively impacts the overall biological functions of plants (Figure **2**); however, the severity depends on the concentration and duration of exposure, plant species, and growth stages [61]. Salinity stress enhanced ROS generation, damaging the cell membranes, proteins, and nucleic acids and ultimately hampered growth, biomass productivity, and yield [62, 63, 64, 65]. Soil microbial biomass and various enzymatic activities are also affected under salinity stress which deteriorates the soil quality, fertility, and overall crop production [66, 67]. Plants ensure their survival and growth against deleterious abiotic stresses [68]; e.g., Wheat ensures their survival under salinity stress on the cost of yield and biomass [69]. Plants alleviate the negative impact of salinity stress by evolving protective mechanisms like antioxidant defense systems [70]. It is a cascade of different enzymatic and non-enzymatic antioxidants which helps the plants to overcome salinity-induced oxidative damages [71]. The second defense mechanism is osmotic adjustment by synthesizing various organic solutes [10]. Proline, GB, amino acids, and sugars are the organic molecules that maintain the osmotic balance of cells and protect plant organelles by scavenging ROS [72]. Osmolytes also boost photosynthetic efficiency and enhance the antioxidant machinery for better growth and productivity under salinity stress [73].

The exogenous application of GB has beneficial effects on various plant species under salinity stress (Table **1**). Applying GB (100 mM) to wheat plants enhanced the relative water content and Fv/Fm under salt stress [74]. GB-based bio-stimulants resulted in better photosynthesis and growth and reduced $Na^+$/ $Cl^-$ uptake by roots under moderate to high salinity stress in tomato plants [75]. The benefits of GB (25 mM / 50 mM) against salinity stress of 50 mM / 100 mM are evident in enhanced antioxidant defense, maintenance of photosynthetic pigments, relative water content, yield, and high $K^+/Na^+$ ratio [76]. Foliar application of GB (0 mM, 25 mM, 50 mM) on onion plants against the 4.80 dS $m^{-1}$ salt stress increased the shoot length, fresh weight, dry weight, bulb yield, and water use efficiency [77]. GB enhances the total soluble sugar, $Ca^{2+,}$ and $K^+$ concentration and photosynthesis processes of cucumber plants [78]. Pretreatment of GB improved growth and increased antioxidant activity [79]. 25 mM GB improved dry matter content by 44% under 100 mM NaCl treatment [80], along with increased phenolics and antioxidants [80]; it also improved the physiological characteristics and antioxidant defense systems of basil plants under various salinity levels [81]. An enhancement in yield by

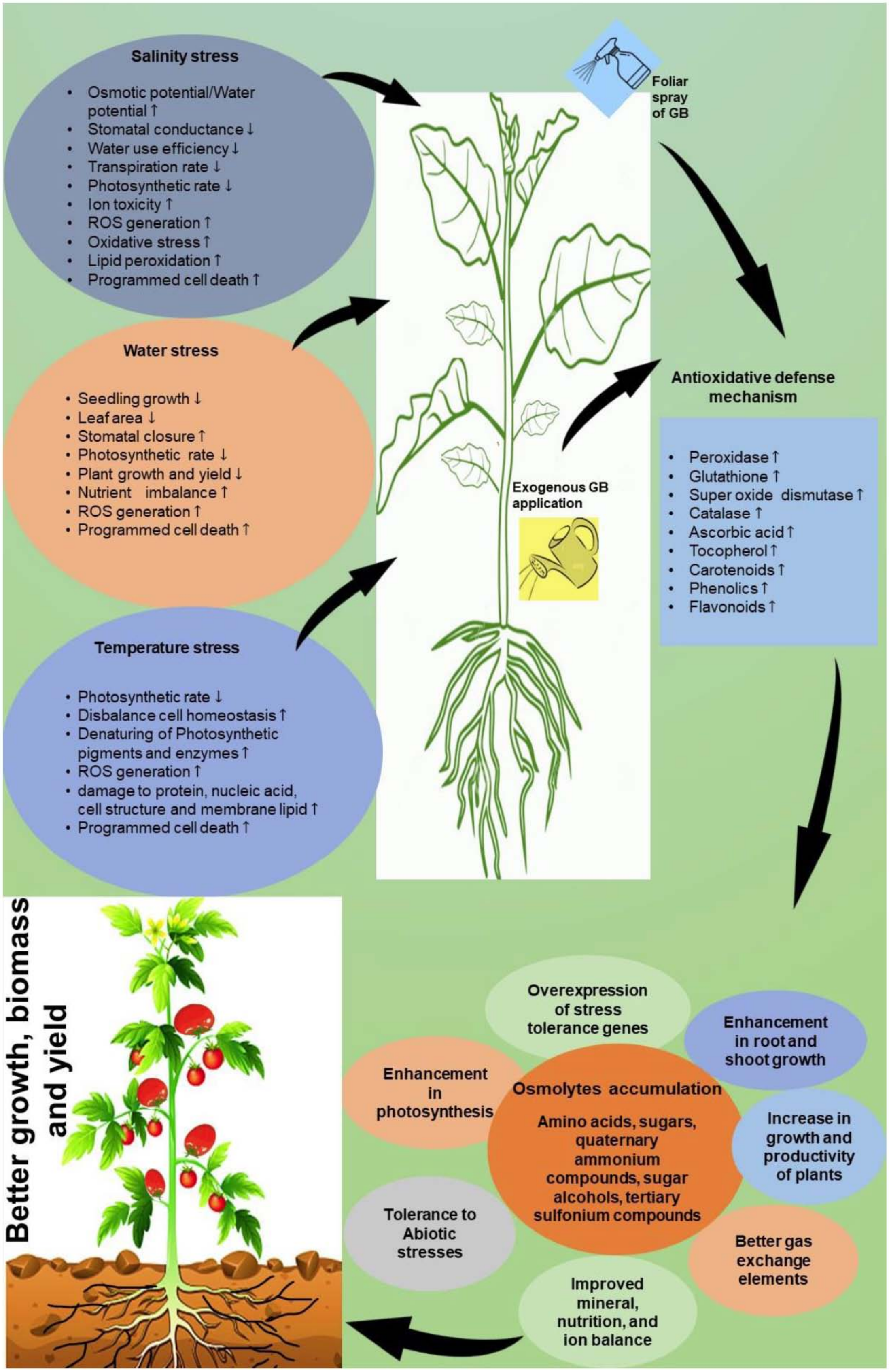

**Figure 2:** Schematic representation for the impact of various abiotic stresses (i.e., salinity, water, and temperature) and defense strategies adopted by the plants through exogenous application of glycine betaine. CMO (choline monooxygenase); BADH (betaine-aldehyde dehydrogenase); ↑ (increase); ↓ (decrease).

**Table 1: Glycine Betaine Induced Tolerance in Plants under Abiotic Stresses**

| Plant | Abiotic Stress | Concentration of Glycine betaine utilised | Beneficial impact of glycine betaine in plants | References |
|---|---|---|---|---|
| Bean | Salinity stress 0 mM, 50 mM, 100 mM NaCl | 25 mM, 50 mM, 50 ml per plant | High $K^+/Na^+$ ratio, low $Na^+$ uptake, increased relative water content, photosynthetic pigment, pod yield and antioxidative defence mechanism | [51] |
| Onion | Salinity stress 4.80dS$^{-1}$ | 0 mM, 25 mM, 50 mM | Increased in shoot length, shoot fresh and dry weight, leaf area, bulb yield, water use efficiency, leaf chlorophyll, relative water content, membrane stability, antioxidative enzymes, osmolytes and decrease in reactive oxygen species. | [52] |
| Wheat | Salinity stress 9.40 to 7.90 dS m$^{-1}$ | 100 mM | High relative water content, high Fv/Fm, increased number of spikes, and grain yield | [49] |
| Cucumber | 0 mM, 50 mM, 100 mM NaCl | 0 mM, 50 mM, 100 mM | Increased total soluble sugar, proline, GB, $Ca^{++}$ and $K^+$ concentration, photosynthetic efficiency and yield. | [53] |
| Strawberry | Salinity stress 34 mM NaCl | 5g L $^{-1}$ | Enhanced yield by 30% | [57] |
| Basil plant | Salinity stress 50 mM, 75 mM, 100 mM NaCl | 50 mM, 100 mM, 200 mM | Improved physiological parameters and antioxidative defence system. | [56] |
| Soybean | 150 mM NaCl | 0, 5, 25, 50 mM | Improved growth and antioxidant capacity | [54] |
| Lettuce | 0, 100 mM NaCl | 0, 5, 10, 25 mM | Increased dry matter content, total phenolics and antioxidants | [55] |
| Tomato | Cold stress 14°C | 10 mmol/L of GB | Enhanced germination rate, germination index, viability of seeds, antioxidative enzymes. | [73] |
| Tomato | Cold stress 4°C | 5 mM GB | Increased electron flow between photosystems, maintained redox potential, protected photosystem from photoinhibition | [74] |
| Banana | Cold stress 7°C | 100 mM GB | Increased contents of antioxidant chlorophyll, soluble sugar, total phenolics, ascorbic acid and glutathione. | [75] |
| peach | Cold stress 0°C | 10 mmol L$^{-1}$ | Increased phenolics, flavonoids, sucrose, and antioxidative- enzymes. | [76] |
| Blood oranges | Cold stress 3°C for 90 days | 15 mM, 30 mM at 30 kPa | Increased antioxidative activity and decreased malondialdehyde content and electrolyte leakage. | [77] |
| Plum | Cold stress 1°C | 2.5 mM, 5 mM | Reduced chilling injury, increased nutritional quality, storage potential and shelf life. | [78] |
| Nanguo pears | Cold stress 0 ± 0.5°C for 120 days | 0.1 mol L$^{-1}$ GB | Decreased browning index, lipid peroxidation, Increased antioxidants and proline. | [79] |
| Sugarcane | Cold stress 15°C, 2 days | 10 mM, GB, 8h | Increased proline and GB, soluble sugars, $K^+$ and $Ca^{++}$ | [80] |
| Cotton | Cold stress, 5°C, 3 days | 400 µL/ml, 14 h | Increased relative water content and decreased cell membrane damage | [81] |
| Peach | Cold stress 0 ± 0.5°C | 10 mM | Increased total soluble solid, organic acid, total free amino acids, compatible solutes, flavour and quality | [82] |
| Wheat | Heat stress 40°C | _ | Increased antioxidative activity, improved water status, and photosynthetic rate | [84] |
| Sugarcane | Heat stress, 42°C | 20 mM, 8 h | Increased soluble sugar, and protected developing tissue. | [80] |

**(Table 1). Continued.**

| Plant | Abiotic Stress | Concentration of Glycine betaine utilised | Beneficial impact of glycine betaine in plants | References |
|---|---|---|---|---|
| Marigold | Heat stress, 39°C | 0.5 and 1 mM, 15 days | Increased transpiration rate and decreased lipid peroxidation. | [85] |
| Green bean | Drought stress 55, 70, 85 and 100% of irrigation | 5, 10, 15, 20 mM | Improved growth parameters and yield | [106] |
| Flax | Drought stress irrigation was withheld water for 5 days | 50 mM and 100 mM _ | Increased endogenous GB, and proline. | [107] |
| Green Chiretta | Drought stress, water deficit 68% of field capacity | 25, 50, and 100 mM | Increase total soluble sugar, osmotic potential, free proline, leaf temperature and crop water stress index. | [108] |
| Spinach | Drought stress, 50% irrigated | 50, 100, 150 µM | Increased catalase activity, proline, protein carotenoids, and chlorophyll. | [105] |
| Tomato | Waterlogging stress, 10 days of waterlogging by blocking the drainage | 50 mM for 25 days | Reduced MDA content, membrane injury, Na accumulation, Increased $K^+$and $Ca^{++}$accumulation | [109] |

GB (glycine betaine); mM (millimolar); µM (micromolar); dS$^{-1}$ (desi siemens per metre); MDA (malondialdehyde).

strawberries under 34 mM NaCl due to GB application [82]. Overall results concluded that GB enhances plants growth and survival by preventing metabolic dysfunctions, reducing $Na^+$, and simultaneously inducing $K^+$ uptake, maintaining a greater $K^+/Na^+$ ratio. It also acts as a potent osmolyte that can be used as a superior tool for reducing salt stress' negative impacts on plants. Plant physiological characteristics and antioxidant defense mechanisms were enhanced by exogenously administered GB.

## Temperature Stress and Glycine Betaine

Temperature stress is one of the major limiting factors that hamper the growth and yield of plants (Figure **2**). The exogenous application of GB enhanced various plant species' temperature stress tolerance capacity (Table **1**). Increased soluble proteins, sugar molecules, and other osmolytes have been recorded in plants under low temperatures [16]. Antioxidative enzyme activities, electrolyte leakage, lipid peroxidation, and ROS also increased in many plant species under low-temperature stress [83, 84]. Loss in biomass, chlorophyll content, and genome templet stability was observed for pepper cultivars under low temperatures; whereas proline content, catalase activity, and DNA methylation were increased [85]. Pepper plants exposed to low temperatures (8°C) reflected an increase in ROS and reactive nitrogen species (RNS) for the first day. At the same time, cold acclimation has been observed during the second and third days of exposure via increased concentrations of enzymatic and non-enzymatic antioxidants [86]. Low-temperature stress is responsible for maize's reduced growth and productivity [87], accompanied by reduced leaf size, stem growth, root growth, and imbalanced nutrients uptake [88]. Plant growth hormones such as auxin, gibberellin, cytokinin, ethylene, SA, brassinosteroid, PA$_S$, and nitric oxides modulate the response to chilling stress in maize [88]. Under low temperature, reduction in the mean leaf area index, mean net assimilation rate, harvest index, biomass, and grain yield were observed in wheat [89].

ROS like hydrogen peroxide and superoxide anions are increased due to high-temperature stress in plants. Accumulation of ROS causes lipids peroxidation, protein denaturation, and chloroplast damage [90]. Photosystem I (PSI) show more stability than Photosystem II (PSII) under high-temperature stress [91]. In tobacco and wheat, the high temperature was responsible for the reduced function of PSI [91, 92]. In response to temperature stress, the cascade of antioxidative defense system protect plants against oxidative stress [93].

On the other hand, defense is also maintained through compatible solutes like GB, sugars, and proline [94]. Reduction in overall growth and fruit setting has been observed under temperature stress in tomato plants [95]. Retardation in root growth and photosynthetic rate under heat stress ultimately leads to crop death [96]. High temperature is responsible for alteration in the functioning of PSII along with the electron transport chains [97], and the overall result is a reduction in plant growth and yield.

Priming seeds with GB increased germination rate, germination index, and seed viability in tomatoes under low-temperature stress (14°C) and also controlled the buildup of ROS by enhancing the ROS scavenging system [98]. GB reduces ROS generation and photoinhibition in tomato plants under chilling stress by maintaining cyclic and noncyclic electron flow between the photosystems [99]. Exogenous application of GB was responsible for enhanced antioxidant activity, chlorophyll content, total soluble sugar, total phenolics, ascorbic acid, and glutathione under cold storage conditions with improved shelf-life of bananas [100]. On the other hand, 10 mM GB was sufficient to maintain the storage capacity of peaches under 3°C for 90 days via increased antioxidative activity and reduced lipid peroxidation and electrolyte leakage [101]. The application of GB at 3°C for 90 days resulted in the extended postharvest life of oranges [102]. The utilization of GB-coated chitosan nanoparticles enhanced the endogenous proline and glycine content, which correlates well with the tolerance to chilling stress under cold storage in plums [103].

Similarly, in pears, exogenously applied GB was helpful for the reduction of the flowering index at 0°C for 120 days [104]. In sugarcane, 10 mM of GB was responsible for enhanced osmolytes, total sugars, $K^+$, and $Ca^{2+}$ under 15°C for two days [105]. Reduced cell membrane damage and increased relative water content have been reported in cotton due to 400 µL/ml GB application for 14 hours under 5°C for three days [106]. Exogenous GB enhanced peach fruits' flavor, quality, and tolerance capacity via increased accumulation of the total soluble solids, organic acids, free amino acids, and compatible solutes [107].

GB protects the photosystems, proteins, nucleic acids, and lipids from degradation and enhances growth via improved tolerance against heat stress [108]. Protection of photosystems from photoinhibition was achieved through GB application under heat-stressed wheat plants [109]. Reduction in the number and area of mesophyll cells hampered the formation of new buds and leaves under heat-stressed sugarcane. In contrast, GB application increased total soluble sugar, $k^+$, and $Ca^{2+}$ content and reduced ROS providing better tolerance against heat stress [105]. Increased transpiration and decreased lipid peroxidation were observed for marigold (39°C) after applying exogenous GB for 15 days [110]. GB protected PS II from damage via enhanced synthesis of D1 protein [111]. Thus, GB has proven beneficial for plants under temperature stress, supporting optimal development and survival (Figure **2**). Experimental findings related to this aspect suggest that GB increases the capacity to withstand temperature stress by increasing the accumulation of total soluble solids, organic acids, free amino acids, and suitable solutes. It improves growth via increased tolerance to heat stress and prevents the degradation of photosystems, proteins, nucleic acids, and lipids. Therefore, GB acts as potential SMs and is beneficial for plants under temperature stress, promoting optimal growth and survival.

## Water Stress and Glycine Betaine

Water stress is a combined effect of waterlogging and drought stress, interferes with normal metabolism via the overproduction of ROS and ultimately lead to cell death (Figure **2**). Waterlogging interferes with plants' growth and developmental processes by inhibiting aerobic respiration and energy metabolism [112]. It creates hypoxic conditions near the root zone, hampers root oxygen availability, and leads to plant death [113]. Waterlogging and anaerobic conditions are responsible for increased ROS which lead to programmed cell death in plants [114]. Reduced stomatal activity, chlorophyll production, photosynthetic rate, vegetative and reproductive growth, and eventually yield were all effects of water stress [115]. Plants develop survival strategies by shifting metabolic processes toward low-energy fermentation processes [116]. The interaction of various biomolecules, soluble sugar compounds, and phytohormones produced by plants results in improved antioxidative defense mechanisms [117]. Plants produced aerenchyma and a number of adventitious roots to help them survive under water-stressed environment [118]. Waterlogging is mainly responsible for reduced cell permeability**,** root activity, respiration process and increased oxidative damage, which hampers the stomatal functioning, chlorophyll synthesis and photosynthesis [119, 120]. It also enhanced the denitrification process that interferes with plants' nitrogen and carbon metabolism, causing a decrease in soluble sugars and nitrogen availability to plants [121]. Waterlogging enhances the leaching of mobile nutrients, due to which plants face mineral deficiency [119]. In summer maize, waterlogging was responsible for decreased chlorophyll content, ear length, ear diameter, plant height, leaf area, grain weight, and increased bald tip length [122].

Drought stress is one of the major challenging issues to plant growth and productivity [123]. It is responsible for reduced chlorophyll, gas exchange, and relative water content due to increased ROS and lipid peroxidation [124]. Higher ROS accumulation damage biomolecules like proteins, nucleic acids, lipids, and photosynthetic pigments. In response to drought stress, plants altered their osmotic potential, water potential, and accumulated antioxidative enzymes such as SOD, CAT, peroxidase (POD), and ascorbate peroxidase (APX) [125]. Plants synthesize osmolytes like proteins, proline, GB, phenolics, flavonoids, and soluble sugars [126] that helps to alleviate drought stress. Phytohormones play an important role in signaling and other developmental processes which provide tolerance to abiotic stresses [127]. Reduced seed germination, blooming, plant height, leaf area, relative water content, stomatal conductance, net photosynthesis, total biomass, and yield are all results of drought stress [128].

The exogenous application of GB plays an important role in protecting plants under water stress (Table **1**). It protects plants by adjusting osmotic pressure, gene regulation, and other cellular and subcellular responses. It also enhances the endogenous GB accumulation in plants, which provides better protection under various abiotic stresses [129]. GB maintained the cell protein concentration, water status, cell membrane integrity, antioxidative activity, and photopigments of plants under water stress [130]. Exogenous GB has been used to alleviate the negative impact of water stress and improve growth parameters like pod number, pod length, pod thickness, plant height, number of leaves, number of branches, and total fresh weight of green beans [131]. Exogenous GB spray enhanced the buildup of endogenous GB content in flax, enhancing its capacity to withstand drought stress [132]. In green chiretta, 50 mM and 100 mM GB applications under drought stress led to enhanced total soluble sugars, osmotic potential, free proline, leaf temperature, and crop water stress index [133]. 50, 100, and 150 µM GB applications stimulated spinach's catalase activity, proline, proteins, carotenoids, and chlorophyll content under drought conditions [130]. Under waterlogging, 50 mM GB application for 25 days on tomato plants was responsible for the higher accumulation of $K^+$ and $Ca^{2+}$ along with decreased membrane injury [134]. Thus, the GB has been proven beneficial for better growth and yield of plants under water stress, as shown in Figure **2**. The experiments suggested that under water stress, GB sustains plants' cell protein concentration, hydration status, and antioxidative activities along with the integrity of cell membranes and photopigments. Further, GB has been used to maintain osmotic pressure, cellular and subcellular reactions, and ultimately gene regulation to reduce the detrimental effects of water stress and functions as a potential secondary metabolite.

## Crosstalk between Glycine Betaine and Phytohormones

GB provides tolerance against various abiotic stresses via activating antioxidant machinery to detoxify ROS molecules and maintains the cellular osmoticum of plants. These complete processes require strong regulation and intrinsic interaction between several biomolecules and signaling cascades (Figure **3**). Phytohormones are important biomolecules that regulate normal physiological activities and ensure better growth and development of plants [135]. These biomolecules provide tolerance against several abiotic stresses via complex signaling cascades, from receiving a signal to activation of several stress-specific genes [136]. Phytohormones provide a better microenvironment for plant growth and development by establishing proper source and sink relationships and resource partitioning to different organs based on their need to acclimatize under adverse environmental conditions [137]. Accumulation of GB is positively correlated with the accumulation of stress phytohormones like ABA, SA, JA, and $PA_S$ and vice versa. All the phytohormones and biomolecules function in a very regulated and correlated manner, ensuring plant growth and survival under various abiotic stresses, as shown in Figure **3**.

### Abscisic Acid

ABA is one of the important stress phytohormones, synthesized in roots and other tissues under various abiotic stresses and transported to leaves and other plant parts to check stomatal closure and water loss [138]. Via activating stress-responsive genes, which are involved in the biosynthesis of a number of SMs, osmolytes, and antioxidants, ABA provides tolerance to abiotic stresses [139]. Betaine aldehyde dehydrogenase (BADH) transcription is upregulated in leaves and roots in response to ABA, which causes GB accumulation in plants [140]. Heat stress enhanced the endogenous ABA, which induced BADH gene transcription and GB accumulation in plants [141]. Exogenous ABA application is well correlated with the accumulation of GB in barley plants exposed to salinity, drought, and low-temperature stresses [142]. The exogenous fluridone application inhibits the biosynthesis of ABA and GB in plants through

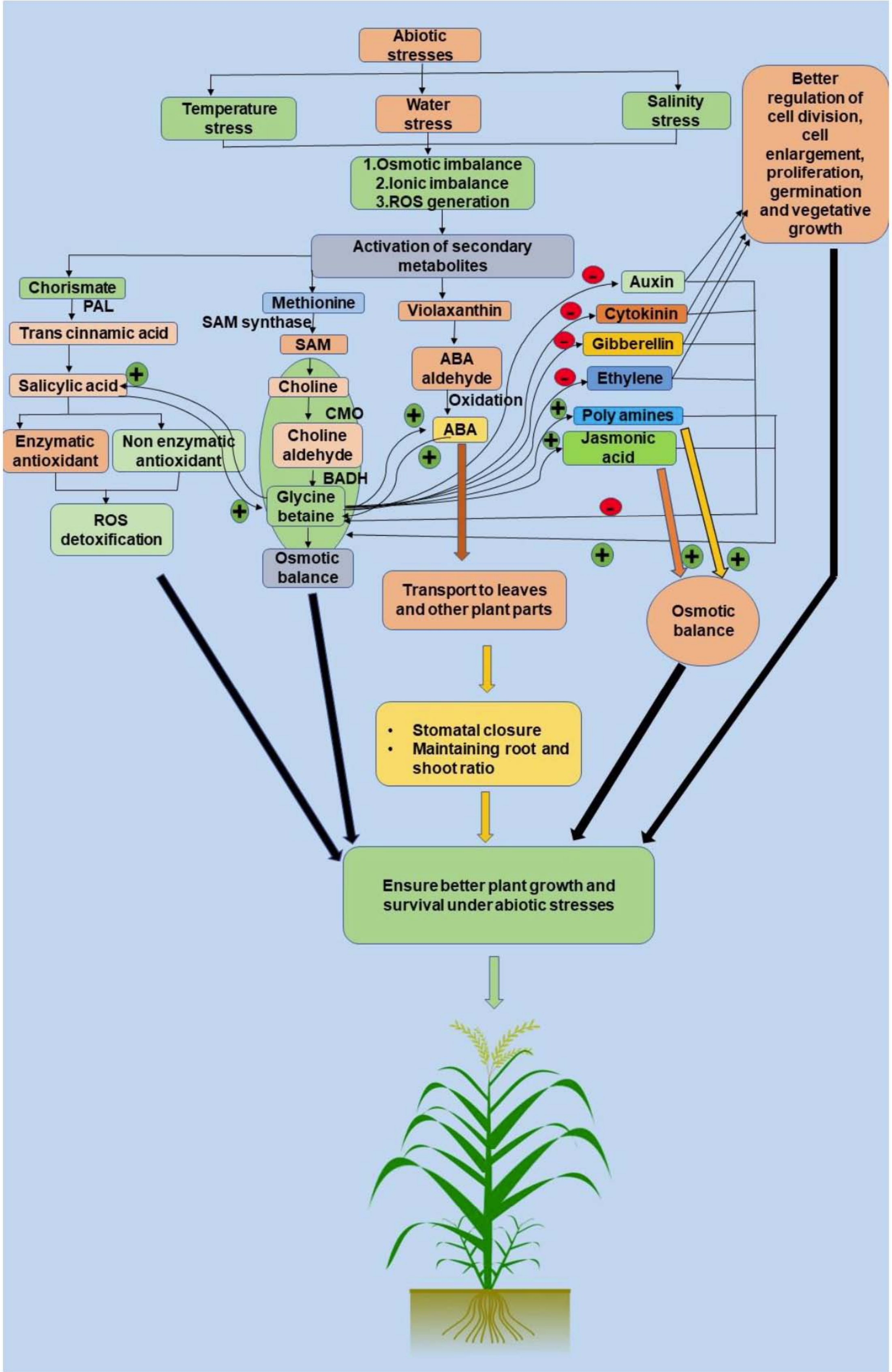

**Figure 3:** Crosstalk between glycine betaine with phytohormones during various abiotic stresses (i.e., salinity, water, and temperature) in plants. ABA (Abscisic acid); PAL (Phenylalanine ammonia-lyase); SAM (S-Adenosyl methionine); CMO (Choline monooxygenase); BADH (Betaine aldehyde dehydrogenase); + (positive correlation); - (negative correlation).

alteration in carotenoids biosynthetic pathway in corn [143, 144]. Studies suggested a strong and positive correlation between ABA and GB, which is beneficial for the survival of plants under abiotic stresses (Figure **3**).

### Salicylic Acid

SA provides immunity against various abiotic stresses like salinity, drought, temperature, UV radiations, heavy metals, etc., via activating systemic acquired resistance in plants. It mediates signaling with other phytohormones to stimulate the accumulation of osmolytes and strengthen defense mechanisms in plants under abiotic stresses [145]. Pretreatment of SA enhanced BADH gene expression and GB accumulation under osmotic stress [146]. Under salt stress (50 mM NaCl), increased endogenous GB was caused by the exogenous administration of SA in mung bean**,** resulting in improved photosynthesis, antioxidative defense, water potential, and growth indices. On the other hand, a decrease in lipid peroxidation, $Na^+$, $Cl^-$ buildup, and lipid peroxidation have been observed [147]. Exogenous application of SA enhanced the endogenous GB, proline, soluble sugars, antioxidative enzymes, and chlorophyll, which further improved water relation and overall yield under various abiotic stresses [148]. A positive correlation between SA and the biosynthesis of GB has been observed in several studies, and it is well correlated with the tolerance mechanism of plants against various abiotic stresses (Figure **3**).

### Jasmonic Acid

JA is involved in plants defense against various abiotic stresses like salinity, drought, temperature, heavy metals, and flood by synthesizing various osmoprotectants like GB and better antioxidative defense mechanisms [149]. The coordination of JA and SA has been observed in plants' defense against UV-B stress [150]. Exogenous JA induced antioxidative enzymes and reduced oxidative stress in maize plants under drought stress [151]. Similarly, JA reduced lipid peroxidation, increased antioxidants, and improved the $K^+$ content of plants under salt stress [152]. Pre-treated soybean seeds with JA enhanced salt tolerance via improved osmoprotectant accumulation [153]. Exogenous JA application increased the endogenous GB in *Brassica rapa* L. [154]. Thus, the JA and GB play an important role in providing tolerance to plants during abiotic stresses (Figure **3**).

### Ethylene

Ethylene is an important gaseous plant hormone that regulates plants growth under abiotic stress like salinity, drought, flood, temperature, heavy metals, and UV radiation. It enhances the antioxidative defense system of plants, reduces oxidative stress, and increases plants' photosynthetic rate and yield [155]. GB and ethylene interact together, as shown in Figure **3**, to provide tolerance against salinity stress in plants [156]. Exogenous application of SA enhanced GB accumulation via increased methionine biosynthesis and decreased ethylene biosynthesis [155]. An increase in GB biosynthesis enhanced the photosynthetic rate, growth, and yield of stressed plants via upregulating antioxidative defense pathways [155]. Endogenous ABA and SA is well coordinated for the biosynthesis of GB in the chloroplasts [157]. Increments in GB accumulation and reduction in ethylene content have been observed in plants under salt stress [158]. It has been found that plant species that accumulate low amounts of ethylene tend to synthesize more GB to provide tolerance against various abiotic stresses [159].

### Polyamines

$PA_S$ are small, low molecular weight, plant growth regulatory biomolecules produced during various plant metabolic processes [160]. PAS are helpful in maintaining plants' normal growth and development during various abiotic stresses like salinity, temperature and water stresses (Figure **3**). They play an important role through exogenous application along with endogenous levels in plants. $PA_S$ favour growth and development by preventing the degradation of nucleic acids, proteins, and lipids and also enhance protein folding during stress conditions. They promote SMs accumulation by serving as precursor molecules [161]. Similar to GB, $PA_S$ work as compatible solutes; both molecules coordinate well to regulate the osmotic balance of cells during abiotic stresses [162]. Priming of salt stressed-seedlings of rice with $PA_S$ reflected enhanced BADH1 expression in the shoots and roots [163]. Exogenous application of spermidine on *Raphanus sativus* seedlings improved the GB and proline contents under Cr stress [164].

## CONCLUSIONS AND FUTURE PERSPECTIVES

Abiotic stresses potentially threaten agricultural productivity and food security under current and predicted climate change globally. GB is one of the important SMs and functions as a potential osmolyte during abiotic stresses in plants. The defensive roles of GB against various abiotic stresses are well depicted through the exogenous application or when stimulated endogenously in plants to ensure better growth and development along with their survival under adverse environmental conditions. The mechanism of action of GB against abiotic stresses can be divided into three different phases, i.e. (i) GB acts as a potential osmolyte that promotes the accumulation of other compatible solutes and maintains the water status of the cell via balancing cellular osmoticum and thus provide defense against osmotic stress. (ii) GB is helpful for the induction of antioxidative defense mechanisms to ensure proper quenching of ROS in order to reduce oxidative damage in plants. (iii) GB positively coordinates with other biomolecules for expressing stress-related genes to enhance the tolerance capability of plants under various abiotic stresses. Researchers throughout the globe are continuously involved with experiments to develop tolerant cultivars against abiotic stress via transferring the gene for glycine betaine biosynthesis (genetic engineering) in the sensitive cultivar and to pinpoint the precise mechanism by which GB confers tolerance at the physiological and molecular levels to the plants. In the scenario of climate change, this helps highlight the issue of global food security.

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## CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

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