

SPECIAL ISSUE ARTICLE

Developing climate-resilient crops: improving plant tolerance to stress combination

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Received 26 July 2021; revised 22 August 2021; accepted 31 August 2021; published online 5 September 2021.

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SUMMARY

Global warming and climate change are driving an alarming increase in the frequency and intensity of different abiotic stresses, such as droughts, heat waves, cold snaps, and flooding, negatively affecting crop yields and causing food shortages. Climate change is also altering the composition and behavior of different insect and pathogen populations adding to yield losses worldwide. Additional constraints to agriculture are caused by the increasing amounts of human-generated pollutants, as well as the negative impact of climate change on soil microbiomes. Although in the laboratory, we are trained to study the impact of individual stress conditions on plants, in the field many stresses, pollutants, and pests could simultaneously or sequentially affect plants, causing conditions of stress combination. Because climate change is expected to increase the frequency and intensity of such stress combination events (e.g., heat waves combined with drought, flooding, or other abiotic stresses, pollutants, and/or pathogens), a concentrated effort is needed to study how stress combination is affecting crops. This need is particularly critical, as many studies have shown that the response of plants to stress combination is unique and cannot be predicted from simply studying each of the different stresses that are part of the stress combination. Strategies to enhance crop tolerance to a particular stress may therefore fail to enhance tolerance to this specific stress, when combined with other factors. Here we review recent studies of stress combinations in different plants and propose new approaches and avenues for the development of stress combination- and climate change-resilient crops.

Keywords: climate change, global warming, abiotic stress, biotic stress, stress combination, multifactorial stress combination, acclimation strategies, crop plants, yield.

INTRODUCTION

The constant increase in the accumulation of greenhouse gases, in particular CO₂, has driven a dangerous rise in global land surface and ocean temperatures, termed global warming. This process is causing an increase in the frequency and intensity of drought episodes, heat waves, cold snaps, and flooding, termed climate change (Anderegg et al., 2020; Gathen et al., 2021; Hassani et al., 2020; Houtan et al., 2021; IPCC, 2014; Raymond et al., 2020; Steg, 2018; Zandalinas et al., 2021a; Figure 1). Although

climate change is thought of as a global phenomenon, its manifestation as changes in short- or long-term weather trends, are different in different regions around the globe and could result in the simultaneous occurrence of two or more different abiotic stress conditions (Figure 1a). For example, over the last several years, large areas of the US West were subjected to extreme drought stress combined with heat waves, while many areas of the US Midwest were subjected to flooding and high temperatures. In contrast, many areas in Australia and Northern Africa

were subjected to drought, high salinity, and high temperatures (Figure 1a; www.climate.gov, NOAA; IPCC, 2014; National Drought Mitigation Center; www.droughtmonitor.unl.edu/). These regional climate conditions are frequently combined with harsh soil conditions, including nutrient deficiency, soil salinity, extreme pH, and high levels of different environmental pollutants (e.g., heavy metals, microplastics, herbicides, pesticides, antibiotics, and persistent organic pollutants; Zandalinas et al., 2021a; Figure 1b). In addition, many pathogen and pest outbreaks have been linked to changes in climate trends, such as increases in the frequency and intensity of drought episodes, heat waves, or flooding events (Hóðar et al., 2012; Jactel et al., 2019; Markham and Greenham, 2021; Phophi et al., 2020; Salih et al., 2020). While each of the different abiotic or biotic stresses described above could cause a serious threat to agricultural production, the possible combinations of different stresses occurring because of the multifactorial nature of climate change could pose an even greater threat to major crops, global food production, and food security (Figure 1; Table S1; Alkorta et al., 2017; Jarsjö et al., 2020; Liess et al., 2016; Lobell and Gourdji, 2012; Rillig et al., 2019a; Suseela and Tharayil, 2018; Zandalinas et al., 2021a). A recent study suggested, for example, that the global production of 10 major crops, including barley, cassava, maize, oil palm, rapeseed, rice, sorghum, soybean, sugarcane, and wheat, has already been affected by climate change, and although variability among crops and regions occur, overall consumable food calories of these 10 crops has been reduced by about 1% (Ray et al., 2019).

Because climate change is likely to increase the exposure of many different crops and trees to conditions of stress combinations (Figure 1), it is important to understand how different stresses interact and affect plant growth, yield, and survival. To date, many studies have focused on plant responses to a single abiotic or biotic stressor, or to simple stress combinations of two or at the most three different stress conditions (e.g., water-deficit stress and heat, salinity and heat, water-deficit stress and salinity). These studies revealed that the plant response to a given stress combination is often unique, and could not be predicted from the plant response to each of the different stress conditions applied individually (e.g., Rizhsky et al., 2002, 2004; Mittler, 2006; Mittler and Blumwald, 2010; Prasch and Sonnewald, 2013; Suzuki et al., 2014; Shaar-Moshe et al., 2017, 2019; Zhang and Sonnewald, 2017; Balfagón et al., 2019a; Zandalinas et al., 2020a). Consequently, predicting the effects of climate change is likely to be challenging. Climate change simultaneously affects many different environmental conditions (Figure 1) and could result in conditions of stress combination, on plant growth and development, plant reproduction, and the interactions of plants with other

organisms (including the soil microbiome). It is therefore important to focus current and future research efforts on the study of plant responses to stress combinations, as well as to increase the proportion of stress studies conducted with plants growing in the field and subjected to stress combinations. Unraveling the complexities of plant responses to stress combinations could therefore facilitate the development of climate-resilient crops, improving global food production and securing our future food supply. Here, we highlight the importance of studying stress combinations in plants, propose different methods to develop plants with enhanced tolerance to stress combination and climate change, and discuss different physiological and molecular mechanisms involved in the acclimation of plants to the complex and multifactorial nature of climate change.

PHYSIOLOGICAL AND METABOLIC EFFECTS OF STRESS COMBINATION ON PLANTS

Stress causes a disruption in plant homeostasis affecting key metabolic and physiological processes, limiting energy production, and endangering cellular integrity. To counter the effects of stress, plants must rapidly adjust their metabolic and physiological responses and create a new state of homeostasis in a process termed acclimation (e.g., Walters, 2005). Over longer periods, plants may also alter their anatomy and/or growth and reproduction strategies in a process termed adaptation (Bohnert et al., 1995). Because different stresses may affect plants differently, the acclimation or adaptation responses of plants to each different stress condition might require a different strategy. For example, during drought plants close their stomata to prevent water loss (Hsu et al., 2021; Nilson and Assmann, 2007; Sun et al., 2014), but during heat plants open their stomata to enhance transpiration and cool their leaves (Figure 2a; Zandalinas et al., 2016a, 2020a; Zhou et al., 2015). Each different stress might therefore induce in plants a different acclimation and/or adaptation response, and these could have shared or different components. The main problem plants face during stress combination is that the two different stresses simultaneously affecting the plant could require different and sometimes opposing physiological and metabolic responses. Using the example of drought and heat stresses, when combined, these two different stresses require opposing stomatal responses. Under conditions of stress combination, the plant might therefore prioritize one acclimation/adaptation strategy over the other, use a blend of the two responses, and/or use a completely new strategy. The exact choice of which acclimation/adaptation strategy to use during stress combinations is likely to be impacted by the intensity of each individual stress affecting the plant (i.e., which stress level is stronger), as well as by the timing in which they impact the plant (i.e., which stress was first to affect). In the past several years, researchers have begun to dissect the physiological

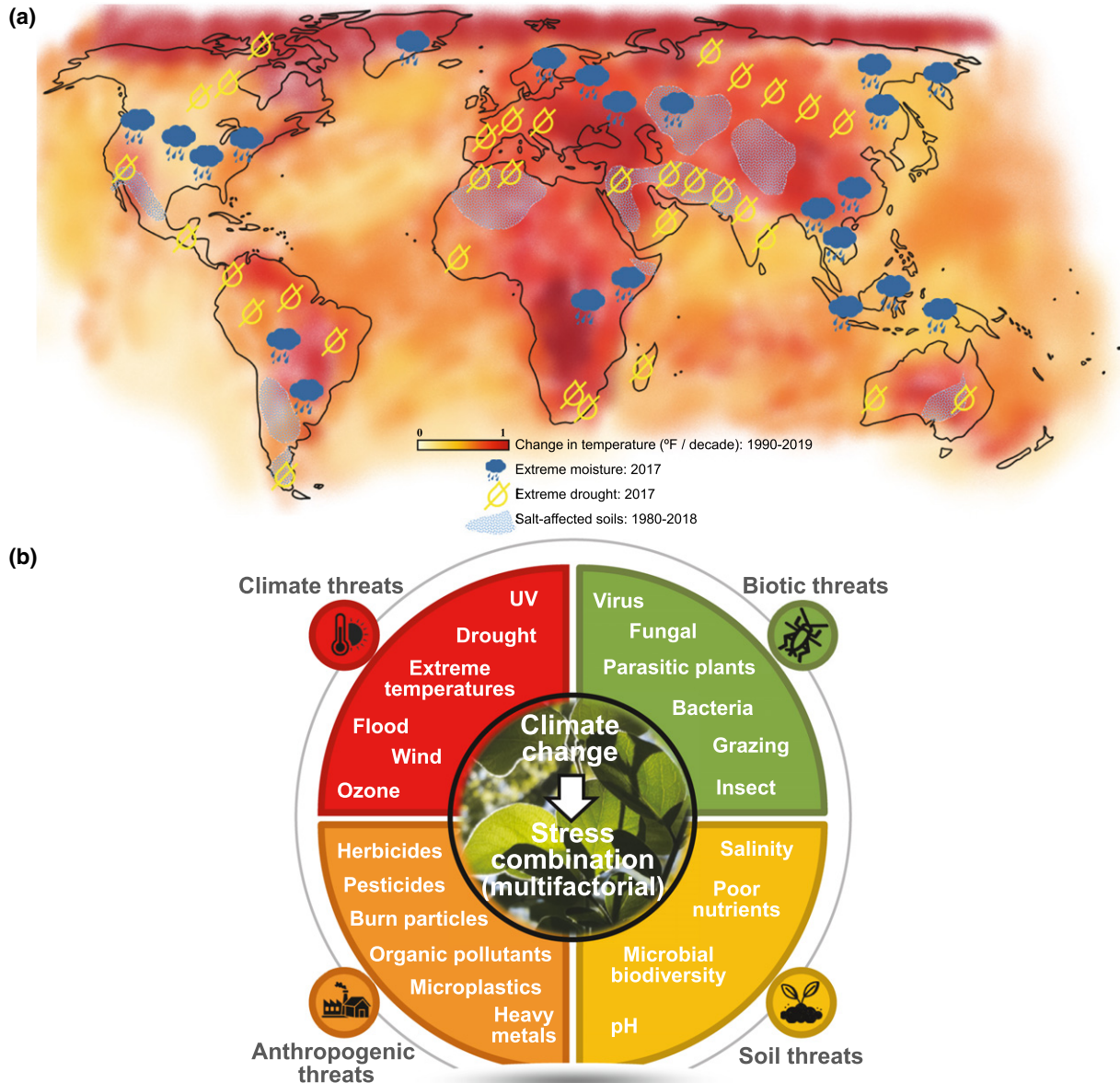


Figure 1. Global warming and climate change are likely to subject crops, trees, and other plants to the sequential or simultaneous effects of stress combinations.

(a) The manifestation of climate change is different in different regions around the globe and could include the simultaneous or sequential occurrences of two or more different stresses, including heat waves, flooding, drought, and/or salinity. Data were obtained from www.climate.gov, NOAA and Hassani et al. (2020).

(b) Potential stress combinations could involve different biotic factors (e.g., virus, bacteria, insect, etc.), climate change-driven weather events (e.g., flooding, extended droughts, heat waves, etc.), man-made anthropogenic stresses (e.g., pesticides, antibiotic, heavy metal, etc.), and/or soil-associated stress conditions (e.g., nutrient deficiency, salinity, decreased microbial diversity, etc.). In different combinations, these environmental stress conditions could negatively impact yield and cause food, feed, and fiber shortages. Adapted from Zandalinas et al. (2021a).

and metabolic responses of plants to stress combinations. Below we will review some of these studies.

Photosynthesis under abiotic stress combination

Photosynthesis is highly susceptible to stress combination, with several studies demonstrating that photosynthetic efficiency and transpiration rates decrease under conditions of water-deficit, salt, and/or heat stresses occurring

together (Perdomo et al., 2017; Zandalinas et al., 2016a,b; Zlatev and Lidon, 2012). A combination of drought and heat, for example, causes a severe reduction in photosynthetic activity (higher than the effects of drought or heat applied alone). This additive effect was demonstrated for *Arabidopsis* (Rizhsky et al., 2004; Zandalinas et al., 2016a), tobacco (Rizhsky et al., 2002), soybean (Cohen et al., 2021a; Jumrani and Bhatia, 2019), lentil (*Lens culinaris medikus*)

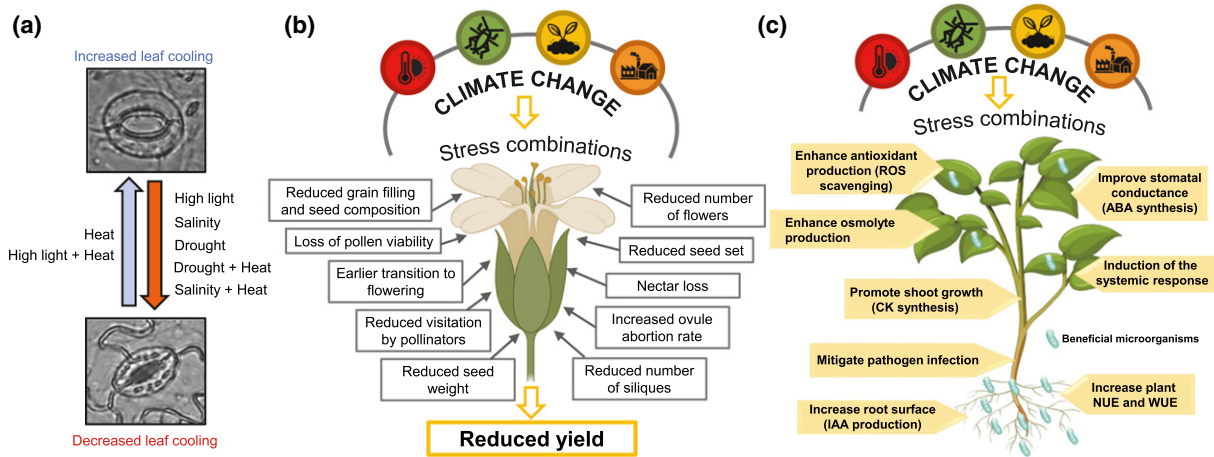


Figure 2. Effects of different stress combinations on stomata and reproduction processes, and the beneficial effects of the plant microbiome. (a) Effects of individual stresses and different stress combinations on stomatal regulation in plants. Modified from Balfagón et al. (2020). (b) Climate change-driven stress combinations negatively affect plant reproduction, resulting in reduced yields. Some of the reproductive processes affected by climate change include pollen maturation, germination and overall viability, fertilization, embryogenesis, seed filling, and plant–pollinators interactions. (c) Schematic overview of some of the beneficial effects of the plant microbiome that could potentially mitigate the impacts of global warming and climate change on plants. ABA, abscisic acid; CK, cytokinin; IAA, indol-acetic acid; NUE, nitrogen-use efficiency; ROS, reactive oxygen species; WUE, water-use efficiency.

(Sehgal et al., 2017), chickpea (Awasthi et al., 2014), tomato (Zhou et al., 2017), maize (Hussain et al., 2019), wheat (Perdomo et al., 2015), and the perennial grass *Leymus chinensis* (Xu and Zhou, 2006). It is thought that this effect results from a combination of two different processes, i.e., (i) a decrease in carbon assimilation rates, due to stomatal closure, and (ii) the negative effects of high temperature on photosystem II integrity (Chen et al., 2018; Gupta et al., 2021; Li et al., 2020). In addition, it was proposed that a combination of drought and heat stress causes a specific decrease in the steady-state level and functionality of different DNA–protein conglomerates called chloroplast nucleoids (Shaar-Moshe et al., 2017). In contrast to the additive negative effects of drought and heat stress combination on photosynthesis, during a combination of salt and heat stress tomato plants prioritize heat stress responses over salinity responses (Colmenero-Flores and Rosales, 2014; Rivero et al., 2014). The effects of salinity and heat combination on photosynthesis is therefore similar to the effect of heat alone, and the opening of stomata during this stress combination (a heat-driven response) allowed plants to increase CO₂ assimilation rates and improved the overall response of plants to the stress combination. In the last several years, different breeding and engineering avenues for the improvement of photosynthetic efficiency in crops growing under field conditions were proposed (Ambavaram et al., 2014; Batista-Silva et al., 2020; Kromdijk et al., 2016; Reynolds et al., 2021; Rooijen et al., 2017; Simkin et al., 2019). Because photosynthesis plays such an important role in plant responses to stress combinations, it would be interesting to find out

how these modified crops respond to different scenarios of stress combinations. In addition, due to the important role stomata play in plant responses to stress combinations, new strategies for altering stomata regulation and number in different crops subjected to stress combinations could help alleviate the effects of different complex environmental conditions on crop yields.

Stomatal regulation under abiotic stress combination

A combination of abiotic stresses can have different and sometimes opposing effects on stomatal regulation (Rizhsky et al., 2004). During heat stress, stomata open to cool leaves via transpiration, but during drought, stomata close to prevent water loss. During a combination of drought and heat stress, stomata of different plants remain closed, suggesting that drought-driven regulation of stomata overcomes heat stress-driven regulation during stress combination (Carmo-Silva et al., 2012; Rizhsky et al., 2004; Zandalinas et al., 2020a,c). In contrast, during a combination of high light and heat, heat stress-driven regulation of stomata (stomata opening) was found to overcome high light-driven stomata regulation (stomata closure), resulting in stomata opening during this stress combination condition (Figure 2a; Balfagón et al., 2019a). These differences in stomatal regulation suggest that different hormones and/or other regulatory processes could interact to prioritize one type of stomatal response over the other during stress combinations. Studies of hormonal changes during stress combinations involving high temperature and other abiotic stresses such as salinity or high light demonstrated that a coordinated hormonal response to each specific stress

combination is essential to trigger proper stomatal responses and acclimation (Balfagón et al., 2020). Despite its canonical role in regulating stomatal closure, during some stress combinations, the accumulation of abscisic acid (ABA) does not appear to correlate with stomatal closure (Balfagón et al., 2019b; Zandalinas et al., 2016b). A lack of correlation between ABA levels and stomatal closure was found, for example, in citrus plants subjected to the combination of heat and salinity (Balfagón et al., 2019b), or in Arabidopsis plants subjected to a combination of drought and heat stress (Zandalinas et al., 2016b). It was suggested that other signaling molecules could play a role in stomatal responses when salt or drought stress occur at high temperatures (Balfagón et al., 2020). These include H₂O₂ and jasmonic acid (JA) (Murata et al., 2015; Zandalinas et al., 2016a). Accumulation of JA and JA-Ile occurs, for example, under a combination of salinity and high temperatures in citrus plants (Balfagón et al., 2019b), as well as in Arabidopsis plants subjected to the combination of high light intensity and heat stress (Balfagón et al., 2019a). In addition, it was proposed that H₂O₂ could be playing a role in regulating stomatal responses during a combination of drought and heat stress in Arabidopsis plants (Zandalinas et al., 2016a). Co-occurring abiotic stress conditions could therefore trigger the accumulation of different hormones and/or other signaling molecules that would modulate specific stomatal responses (Figure 2a).

Water- and nutrient-use efficiency under abiotic stress combination

Stomata closure during stress is directly linked to a reduction of water-use efficiency (WUE), which is one of the most important parameters in crop responses to osmotic imbalances. WUE is defined as the amount of carbon assimilated as biomass or grain produced per unit of water used by a crop (Hatfield and Dold, 2019). WUE has been studied as a key target for crop improvement for at least a century (Briggs and Shantz, 1913), as water availability is one of the most important environmental factors limiting crop production (Boyer, 1982). Greater temperatures and atmospheric vapor pressure deficit because of climate change are expected to cause an increase in water uptake by plants to maintain growth and reproduction (Grossiord et al., 2017). Initially, an increase in environmental CO₂ concentration could increase WUE, as photosynthesis is expected to increase. However, if plants are also exposed to other stresses that may impair stomatal regulation, WUE could decline. WUE is a complex trait that is affected by many different plant parameters, such as photosynthesis, stomatal and mesophyll conductance, and canopy structure (Leakey et al., 2019), which together with the complexity of the field environment makes the artificial improvement of WUE a challenging task. In most of the studies performed in different crops subjected to a combination of different abiotic

stresses, e.g., drought and heat (Pandey et al., 2021) and drought and salinity (Ranjbarfordoei et al., 2002), a decrease in WUE due to stomatal and non-stomatal limitations was observed (Pandey et al., 2021). Water-use efficiency is also affected by the carboxylation pathway utilized by the plant. C₄ plants have higher intrinsic WUE than C₃ plants, owing to higher photosynthetic rate and lower stomatal conductance (Taylor et al., 2010). Because WUE is such an important trait that affects yield under field conditions, breeding for an improved WUE under stress combination could provide an additional avenue for the development of climate-resilient crops. In a recent study, for example, Lehretz et al. (2021) demonstrated that co-expressing hexokinase 1 from Arabidopsis (AtHKK1) in guard cells and SELF-PRUNING 6A (SP6A) in leaves and stems stimulated tuberization and improved WUE under conditions of drought and heat stress combination in potato. Nitrogen-use efficiency (NUE) is generally defined as the amount of grains produced per unit of available N in the soil. Because climate-driven events of stress combinations such as drought and heat, flooding and heat, or drought and salinity are likely to impact nutrient availability and uptake by crops, studying and improving NUE could be an additional breeding target for generating climate-resilient crops. In addition to breeding, calibrating the amount of N supplied to plants during stress combination could be critical. For example, in a study performed by Ramezanifar et al. (2021), spinach plants grown under a combination of water deficit and salinity were supplemented with different amounts of N (from 0 to 200 mg N kg⁻¹ soil). This study showed that after reaching a certain (critical) level of N supply (100–150 mg N kg⁻¹ soil), further increases in N inputs did not contribute to an increase in yield of spinach subjected to the stress combination (also observed previously by Ramos et al., 2012). Moreover, WUE and NUE decreased under conditions of water deficit combined with salinity and nutrient deprivation. Further studies and breeding efforts are needed to improve WUE and NUE in crops subjected to different stress combinations if we want to achieve our goal of developing crops with enhanced tolerance to climate change.

Stress combination in a high CO₂ environment

When considering the effects of climate change on stress combinations, photosynthesis, WUE, NUE, and other important processes for plant growth and survival, we need to take into consideration the increase in atmospheric CO₂ levels that will accompany these stresses. At high CO₂, stomata of most plants begin to close, decreasing stomatal conductance and transpiration (Zhang et al., 2021). While this response could be beneficial during drought stress increasing WUE, it may not be beneficial for plants subjected to heat stress, or heat stress combined with high light stress that require stomata to remain open (Balfagón et al., 2019a). Because stomatal responses affect

photosynthesis, WUE, NUE, and many other processes in plants, studying the effects of high CO₂ concentrations on plant physiology under conditions of stress combination is critical. The co-occurrence of elevated CO₂ and combined drought and heat was studied in *Arabidopsis thaliana* (Zinta et al., 2014), *Triticum aestivum* (Fitzgerald et al., 2016), *Brassica napus* (Dikšaitytė et al., 2019), wheat (Abdelhakim et al., 2021), and the C3 grassland plant *Trifolium repens* (Roy et al., 2016). These studies showed that high CO₂ levels alleviate the negative impacts of drought and heat combination. The mitigation effect of CO₂ on biomass reduction, photosynthesis inhibition, chlorophyll fluorescence decline, reactive oxygen species (ROS) production, and protein oxidation in *Arabidopsis* plants subjected to the combination of water deficit and heat were associated with reduced photorespiration and increased content of different antioxidant mechanisms (Zinta et al., 2014). High CO₂ was also found to enhance wheat yield in semi-arid environments under heat waves (Fitzgerald et al., 2016), improve plant–water relations and photosynthesis rate at saturating light in *Brassica napus* (Dikšaitytė et al., 2019), increase net photosynthetic rates, and maintain maximum quantum efficiency of photosystem II photochemistry in wheat (Abdelhakim et al., 2021), as well as mitigate the impact of extreme heat and drought on net carbon uptake in the C3 grassland plant *T. repens* (Roy et al., 2016). In contrast, Zhou et al. (2020) showed that tomato plants grown at elevated CO₂ concentration were more sensitive to combined drought and heat stress than those grown at ambient CO₂ due to a higher decrease in net photosynthesis, stomatal conductance, and transpiration, leading to an increased severity of the water-deficit effects. Although, in general, high CO₂ levels promote vegetative growth due to increased CO₂ fixation, altered redox state, reduced photorespiration, and improved WUE, the effects of high CO₂ concentrations on grain quality, and particularly grain protein content could be negative if N availability is limited (e.g., Umnajkitikorn et al., 2020). This is another aspect of high CO₂ and stress combination that needs to be addressed, particularly in light of the potential negative effects of stress combinations on NUE. Because the breath of high CO₂ effects on crops is too vast to cover here, the reader is directed to several excellent reviews on the subject (Ainsworth and Long, 2021; Bright and Lund, 2021; Delabre et al., 2021; Green et al., 2020; Kurganskiy et al., 2021; Lamichaney and Maity, 2021; Lu et al., 2020; Penuelas et al., 2020; Schmidt et al., 2021; Smith, 2021; Soh et al., 2019; Tausz-Posch et al., 2020; Toreti et al., 2020; Wang and Liu, 2021; Wang et al., 2020; Xu et al., 2020).

EFFECT OF STRESS COMBINATION ON REPRODUCTIVE PROCESSES

Sexual plant reproduction requires a complex and highly coordinated set of developmental processes that are tightly regulated and synchronized. Many of these processes, e.g.,

pollen maturation, fertilization, embryogenesis, and seed maturation are highly sensitive to different abiotic stress conditions, such as heat and drought, that could lead to pollen, embryo, or seed abortion (Awasthi et al., 2014; Barnabás et al., 2008; Cohen et al., 2021b; Jiang et al., 2019; Lawas et al., 2019; Prasad et al., 2011, 2015; Ruan et al., 2010; Figure 2b). One of the reasons abiotic stresses impair these processes is the production of ROS under conditions of stress. In reproductive tissues, ROS such as superoxide and hydrogen peroxide play an important signaling role in the triggering of different developmental programs such as the programmed cell death of the tapetum layer, the germination of pollen on the surface of the stigma, or the entry of the growing pollen tube tip through the synergid cells into the egg sack (Barnabás et al., 2008; Kurusu and Kuchitsu, 2017; Mhamdi and Van Breusegem, 2018; Prasad et al., 2015). The production of ROS during these developmental processes is highly coordinated, transient, and restricted to specific tissues. Stress, causing the uncontrolled and unsynchronized accumulation of ROS in many different reproductive tissues, could therefore impair these developmental programs and cause a decrease in fertilization rates, embryogenesis, and overall seed production (Figure 2b; Sinha et al., 2021). The remarkable decreases in yield occurring when different crops are subjected to heat, cold, or drought stress during the flowering season (FAO, Food and Agriculture Organization; <https://www.fao.org/>) demonstrate the vulnerability of reproductive processes to abiotic stresses (Barnabás et al., 2008; Prasad et al., 2015). Moreover, as a recent meta-analysis revealed, the decrease in yield of many crops is further increased when different abiotic stresses are combined during plant reproduction (Cohen et al., 2021b). The combination of drought and heat stress, for example, significantly impacted plant yield by decreasing harvest index, shortening the life cycle of crops, and altering seed number, size, and composition (Cohen et al., 2021b). A more dramatic reduction in seed weight was found in cereals compared with legumes, while the negative effect of the stress combination on harvest index and individual seed weight in legumes was lower than in cereals (Cohen et al., 2021b). During flowering, pollen is particularly sensitive to high temperatures, particularly when combined with drought (Jiang et al., 2019; Ruan et al., 2010). Stigma functionality and fertility are also highly sensitive to combined drought and heat in wheat plants, leading to flower abortion (Fabián et al., 2019). Stress combination also affects the chemical composition and secretion of nectar potentially affecting plant pollinator interactions (Borghi et al., 2019; Glenny et al., 2018; Figure 2b). Frequent increments in light intensity and ambient temperature, which often co-occur during drought episodes, exacerbated the incidence of nectar loss, potentially affecting pollination (Borghi et al., 2019). In addition, it was reported that flora visitation

by pollinators was severely compromised when high CO₂ affected plants together with drought and heat (Glenny et al., 2018). Different abiotic stress combinations alter the use of carbohydrates in anthers of many crop and model species (Borghetti et al., 2019). For example, studies in rice suggested that sugar starvation in floral organs was the underlying factor in reproductive failure in response to the combination of drought and heat (Lawas et al., 2018; Li et al., 2015). Maize kernel abortion was the main reason for the decrease in kernel numbers per spike due to a combination of drought and heat stress, which resulted from the prevention of sugar–starch conversion and limited availability of sugars to kernels during this stress combination (Liu et al., 2020). In rice, while elevated CO₂ had a positive impact at the reproductive and grain filling stages (higher seed-set and improved sugar partitioning to the sink tissue as well as higher photosynthetic rate), a combination of elevated CO₂ and high temperatures led to a significant decline in seed-set and lowered the levels of sink metabolizing enzymes (Chaturvedi et al., 2017). The examples described above reveal that more research is needed into the effects of stress combinations occurring during plant reproduction. Grains, that comprise the majority of our food sources, are the direct result of successful reproduction and must be preserved to ensure food security in the face of our changing climate. In addition to sexual plant reproduction, vegetative propagation of different plants could also suffer from climate change because the process of storage organ formation (e.g., tubers in potato) is highly sensitive to heat stress.

SOIL MICROBIOME AND STRESS COMBINATION

The soil microbiome and its interactions with plants play a key role in plant development, reproduction, and overall health (e.g., plant growth-promoting rhizobacteria; Berendsen et al., 2012; Wei et al., 2019; Figure 2c). In recent years many studies have shown that global warming, climate change, and the increased levels of pollutants in different soils around the world can cause a significant decline in the complexity and composition of the soil microbiome, raising the alarming possibility that this decline would also affect agricultural productivity (Delitte et al., 2021; Rillig et al., 2019b; Sergaki et al., 2018). In addition to the root microbiome, found primarily at the plant rhizosphere, plants also harbor microbiomes on their above-ground surfaces (i.e., their phyllosphere), or internally between their cells (i.e., their endosphere), and all three microbiomes are thought potentially to promote plant growth and enhance resistance to different stresses (Figure 2c). The plant microbiome is dynamic, and its structure and function changes depending on the surrounding environmental conditions (Timm et al., 2018). These changes are thought to be driven by overall changes in the root microenvironment, apoplastic fluid, and cuticle properties,

as well as by the plant strategy of actively seeking cooperation with specific types of microorganisms, particularly during conditions of environmental stress (Bakker et al., 2018). This active process is mediated through the synthesis and excretion of a wide range of chemicals that attract different populations of bacteria (Bakker et al., 2018; Carrión et al., 2019). The resulting interactions are then thought to increase plant tolerance to different abiotic stresses (Fitzpatrick et al., 2018; Hassan and Mathesius, 2012; Liu and Brettell, 2019; Lombardi et al., 2018; Schulz-Bohm et al., 2018; Stringlis et al., 2018). To date, very little is known however about the role of plant–microbiome interactions in plant responses to abiotic stress combinations, particularly under the predicted increase in CO₂ levels (e.g., Tchakounté et al., 2020; Bilal et al., 2020). As discussed below, the use of specialized inoculums targeted for different stress combinations and specific crops should be explored in more detail to increase our chances of producing climate-resilient crops. Because stress combinations can negatively affect soil microbiomes (Rillig et al., 2019b; Rocca et al., 2019; Valliere et al., 2020), care should be taken to match the bacterial/fungal inoculum with the harsh conditions facing the plant, and feasibility studies should be conducted under field conditions in multiple locations.

IMPACT OF ABIOTIC STRESS ON PLANT SUSCEPTIBILITY TO PATHOGENS AND PESTS

The mode and outcome of many plant–microbe interactions, including plant disease epidemics, are profoundly influenced by abiotic factors, such as light, temperature, water availability, and soil nutrient levels (Saijo and Loo, 2020). Additional factors affecting such biotic–abiotic interactions include: plant genotype, age, and developmental stage; pathogen type and infection mode; nature, strength, and timing of abiotic stress; and effect of stress on plant metabolism (e.g., sugar levels and sensing; Saijo and Loo, 2020; Littlejohn et al., 2021). For example, Berens et al. (2019) reported that biotic and abiotic stress responses are differentially prioritized in *A. thaliana* leaves of different ages to maintain growth and reproduction under combined biotic and abiotic stresses. Abiotic stresses, such as high salinity and drought, suppressed immune responses in older rosette leaves through ABA signaling, whereas this antagonistic effect was blocked in younger rosette leaves by GRETCHEN HAGEN 3.12 (GH3.12), a signaling component of the defense phytohormone salicylic acid (SA) (Berens et al., 2019). In general, abiotic stresses increase susceptibility to hemibiotrophic or necrotrophic pathogens, including otherwise weakly virulent facultative pathogens, but reduce susceptibility to biotrophic pathogens (Saijo and Loo, 2020). Many abiotic stress conditions were also shown to alter the transcriptomic response of plants to biotic pathogens and enhance susceptibility to

infection (Atkinson and Urwin, 2012; Suzuki et al., 2014). For example, a transcriptomic analysis of *Arabidopsis* plants subjected to a combination of heat, drought, and virus infection revealed that the stress combination inhibited the expression of transcripts involved in the R-mediated disease response but enhanced the expression of transcripts associated with the heat stress response. These results suggested that abiotic stress factors could alter pathogen-related signaling networks that in turn could suppress defense responses (Prasch and Sonnewald, 2013). The simultaneous impact of water stress and insect herbivory was found, for example, to reduce yields due to improved herbivore performance on water-stressed faba beans (Raderschall et al., 2021). In addition, high temperatures were shown to increase virulence of pathogens in different plants (Cohen and Leach, 2020; Desaint et al., 2020; Zarattini et al., 2021). In rice plants challenged with the fungus *Magnaporthe oryzae*, which causes rice blast, faster pathogen proliferation and increased disease symptoms were observed at high temperatures (Onaga et al., 2017). In *Arabidopsis*, high temperature reduced the expression of the immune receptor FLAGELLIN SENSING 2 (FLS2), which suppresses immunity to the pathogen *Pseudomonas syringae* pv. tomato (Janda et al., 2019). Moreover, it was reported that simultaneous pathogen and high temperature exposures could affect not only pathogen resistance but also heat tolerance. An example could be the higher susceptibility of tomato plants to *Tomato yellow leaf curl virus* (TYLCV) when exposed to heat stress and the compromised heat responses of tomato plants infected by TYLCV (Ghandi et al., 2016). In addition to high temperatures, some studies suggested that drought increased plant susceptibility to pathogen attack (Zarattini et al., 2021). A recent meta-analysis indicated that increased temperatures, CO₂ concentration, drought stress, and nutrient deficiency resulted in greater herbivore consumption, primarily in agricultural systems (Hamann et al., 2021). In contrast to the studies described above, certain abiotic stress conditions enhanced the resistance of plants to biotic stress (Rouhier and Jacquot, 2008). For example, cold stress was shown to confer increased disease resistance against hemi- and biotrophic pathogens (Zarattini et al., 2021). It was reported that short-term exposure to 4°C positively modulated SA-dependent responses at the expense of the JA pathway in *Arabidopsis* (Wu et al., 2019). In addition, drought was suggested to enhance resistance to the bacterial pathogens *P. syringae* DC3000 in *Arabidopsis* plants (Gupta et al., 2016), and to delay powdery mildew disease development in *Alliaria petiolate* (Pandey et al., 2017). The potential of abiotic conditions to alter plant-pathogen and plant-insect interactions highlights the complexity associated with attempts to generate climate-resistant crops. While some strategies may increase tolerance to both abiotic and biotic stresses, some may

increase resistance to abiotic stresses at the cost of enhancing susceptibility to biotic challenges. Further studies are therefore needed to examine the impact of climate change on pathogen and insect populations and diversity, on the general state of plant fitness, and on the different interactions of plants with different pathogens and pests.

MOLECULAR AND REGULATORY RESPONSES OF PLANTS TO STRESS COMBINATIONS

Integration of molecular responses during stress combinations

The co-occurrence of different stresses could result in the activation of conflicting, additive, or completely unrelated molecular responses due to the triggering of different stress-response sensors, signaling cascades, and regulatory networks. In addition, the synthesis of different, and sometimes antagonistic hormones (e.g., JA and SA; Li et al., 2019; Takahashi et al., 2004; Yang et al., 2019), may simultaneously increase during stress combination, leading to conflicting molecular responses. Because different stresses may require different acclimation strategies, plants may prioritize one type of response over the other or use a blend of different molecular and acclimation strategies (Gull et al., 2019; He et al., 2018; Liess et al., 2016; Pandey et al., 2015; Zandalinas et al., 2018). These types of strategies are often revealed by transcriptomics or genome-wide association studies (GWAS) of plants subjected to stress combinations that identify both common and unique responses.

Common signaling pathways and genes that function during different stress combinations as well as during single stresses have been previously described (Pandey et al., 2015; Rizhsky et al., 2004; Shaar-Moshe et al., 2017, 2019; Zandalinas et al., 2021a,b). Such pathways and genes could be associated with universal stress responses, or represent cross-talk between signaling pathways (Prasch and Sonnewald, 2015). For example, 29 transcripts were commonly upregulated in response to drought, heat, and their combination in *Arabidopsis* plants. These included different heat shock proteins and transcripts related to ABA and ethylene signaling (Rizhsky et al., 2004). A large overlap between transcript responses was also found in wheat during a combination of drought and heat stress (Liu et al., 2015). In addition, G-BOX BINDING FACTOR3 (GBF3) was expressed during single and all combined stress conditions of drought, heat, and virus (Prasch and Sonnewald, 2013), as well as during individual and combined heat, salt, and osmotic stresses (Sewelam et al., 2014), indicating that GBF3 could be involved in general stress responses. More recently, a transcriptomic study of *Arabidopsis* plants subjected to a multifactorial stress combination of high light, heat stress, cadmium, acidity, paraquat, and salt (Figure 3), revealed that the steady-state

level of 136 and 127 transcripts was significantly enhanced or suppressed, respectively, in response to all different stress combinations studied. Some of the upregulated transcripts in this group were involved in the regulation of transcription, redox control, stress responses, and ABA responses, whereas some of the downregulated transcripts included were involved in amino acid and carbohydrate metabolism, heme-binding, and glutathione transferase and peroxidase activities (Zandalinas et al., 2021a,b).

In addition to common responses to individual and combined stresses, several transcriptomic studies of plants subjected to different stresses and their combinations identified unique responses specific to stress combinations. For example, a combination of drought and heat altered the expression of over 770 transcripts that were not altered by drought or heat stress (Rizhsky et al., 2004). A transcriptomic study of Arabidopsis plants subjected to drought, heat stress, virus infection, and double or triple combinations of these stresses revealed that many transcripts were specifically upregulated only under the combination of all three stresses (Prasch and Sonnewald, 2013). Other examples include transcriptome studies of drought and O₃ combination (Iyer et al., 2013), and high light and heat combinations (Balfagón et al., 2019a). Interestingly, the

transcriptomics study of Zandalinas et al. (2021b), which focused on different multifactorial stress combinations (Figure 3), identified different stress-response pathways activated in response to many individual abiotic stresses and some of their simple two-stress combinations, but not by specific sets of three or four stress combinations. These, included classical stress-response pathways such as heat shock factors, the unfolded protein response, autophagy, and osmoregulation (Zandalinas et al., 2021b). It was proposed that the function of some of these could be replaced by yet unknown pathways, as the same specific sets of three or four stress combinations resulted in the enhanced expression of large numbers of transcripts with unknown function.

Quantitative trait loci uniquely associated with stress combinations could be identified by GWAS studies. A comprehensive study of the response of 350 different Arabidopsis accessions to 15 different single abiotic and biotic stresses and some of their two abiotic–biotic stress combinations reported cross-correlations between specific single nucleotide polymorphisms and responses to osmotic stress or drought combined with root-knot nematodes (Thoen et al., 2017). Another GWAS study using a collection of 300 tropical and subtropical maize inbred lines

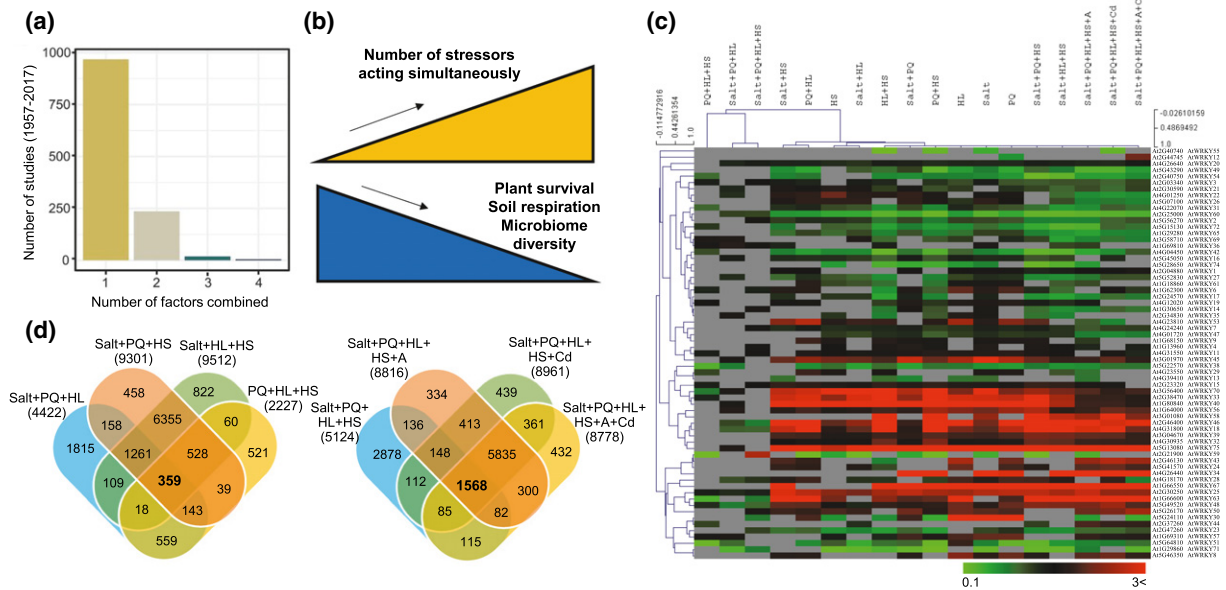


Figure 3. Global warming, climate change, and environmental pollutions present plants with multiple combinations of different abiotic and biotic stresses that could have a detrimental effect on plants, soils, and microbial populations. (a) Multifactorial stress combination is under-represented in studies of plant–stress interactions. Graph shows the number of studies focused on single or multiple stress factors between 1957 and 2017. Adapted from Rillig et al. (2019b). (b) An increase in the number of stressors acting simultaneously (multifactorial stress combination; orange) results in a decrease in plant survival, soil properties, and microbial diversity (blue). Based on the studies of Rillig et al. (2019b) and Zandalinas et al. (2021a,b). (c) Heat map showing the expression level of different WRKY transcription factors in response to multifactorial stress combinations of salt, paraquat, heat stress, high light, acidity, and cadmium. (d) Venn diagrams showing the overlap between genes upregulated in their expression in response to different three-factor stress combinations (left), or four-, five-, and six-factor stress combinations (right). Stresses include salt, paraquat, heat stress, high light, acidity, and cadmium. Transcriptomics data were adapted from Zandalinas et al. (2021b). A, acidity; Cd, cadmium; HL, high light; HS, heat stress; PQ, paraquat.

identified genetic markers for grain yield and flowering time under a combination of drought and heat stress (Yuan et al., 2019). In addition, maize lines with high levels of tolerance to combined drought and heat stress were found in a study conducted using 300 maize inbred lines (Cairns et al., 2013). In this study, tolerance to a combination of drought and heat was associated with genetic markers that were different from those associated with tolerance to individual stresses. Furthermore, in a screen of a tomato introgression line population of 31 lines subjected to a combination of salinity and powdery mildew, a negative impact of salinity on powdery mildew resistance was identified (Kissoudis et al., 2015). Davila Olivas et al. (2017) used a collection of 350 Arabidopsis accessions to explore the natural variation underlying tolerance to different combinations of abiotic and biotic stresses. This study revealed that the number of significant single nucleotide polymorphisms identified in response to stress combination was greater than that in responses to single stresses and identified a list of candidate genes associated with combined drought and herbivore stress.

Integration of stress signaling during abiotic stress combinations

Many different signal transduction mechanisms are involved in stress sensing and signaling in plants. These include different stress-specific sensors/receptor molecules, a large network of calcium channels and pumps that generate different stress-specific calcium oscillation signatures, various ROS sensors, scavengers, and producers that generate different ROS signatures across the different cellular compartments, and multiple networks of kinases and phosphatases that decode the different signals generated and trigger different and sometimes integrated networks of transcriptional regulators/factors (Knight and Knight, 2001; Mohanta et al., 2018; Overmyer et al., 2018; Prasad and Sonnewald, 2015; Raja et al., 2017; Zhu, 2016). Many of these stress signaling-associated proteins, enzymes and channels are further thought to co-localize (e.g., as parts of lipid rafts and/or protein complexes), creating signalosomes that could also be stress-specific (Dietz et al., 2010; Gilroy and Trewavas, 2001). Adding to this complex signaling environment is the fact that many different stress-sensing and signaling events occur in different organelles and involve a complex mode of communication between different organelles and the nuclei (e.g., anterograde and retrograde; Jiang and Dehesh, 2021), and that many other signaling molecules, hormones, and processes, such as S-nitrosylation, ubiquitination, and myristylation are involved in controlling these processes (Martínez-Ruiz et al., 2013; Stulemeijer and Joosten, 2008). Keeping this high level of complexity in mind, it is not surprising that not much is known about how different stress-specific signals (e.g., drought-, heat- or pathogen-specific

signals) are integrated when two or more stresses affect the plant simultaneously (i.e., during stress combination).

In recent years, some examples for the integration of different stress signaling pathways during stress combination were reported. These include different members of several transcription factor (TF) families. For example, certain MYB TFs were found to be specific for a combination of drought and heat stress in Arabidopsis plants (Rizhsky et al., 2004). Analysis of the regulation of different MYB TFs in response to a combination of heat and salt, heat and drought, and heat and high light in Arabidopsis plants revealed that the expression of MYBs 7 and 32 was enhanced and the expression of MYBs 30 and 51 was suppressed, during stress combinations (Zandalinas et al., 2020c). In addition to MYBs, members of the WRKY TF family were reported to respond to several different stress combinations. For example, AtWRKY40 acts antagonistically to AtWRKY18 and AtWRKY60 to enhance Arabidopsis tolerance to salt and osmotic stress via ABA signaling (Chen et al., 2010). In addition, five WRKY family members (WRKYs 50, 53, 42, and 65, and the calmodulin-binding WRKY7 repressor) were found to be expressed in response to combined ozone and drought stress in *Medicago truncatula* plants, suggesting that WRKYs could play a role during this stress combination (Iyer et al., 2013). Another TF family with important roles in plant stress responses is the AP2/ERF family. Within this TF family, DREBs were found to regulate cold, drought, heat, and salt tolerance positively, as well as different stress combinations by regulating different stress-responsive genes (Maruyama et al., 2009; Xie et al., 2019; Zandalinas et al., 2020c). DREB2 TFs are, for example, induced upon drought and heat, and positively regulate stress-response genes such as LEAs and chaperones (Maruyama et al., 2009), whereas members of DREB-A4 family such as HARDY (HRD) and DREB-A6 family such as ERF53, RAP2.4, and RAP2.4A, positively regulate plant responses to drought and salinity (reviewed in Xie et al., 2019). In addition, different ERF subfamilies including ERF-VI, ERF-VII, ERF-XI, and ERF-X have emerged as central players in plant responses to different plant hormones (e.g., ethylene and ABA), metabolic changes, and abiotic stresses in Arabidopsis including flooding, cold, drought, salinity, and heat (Xie et al., 2019). In addition, several AP2/ERF TFs are specifically upregulated in Arabidopsis in response to a combination of high light and heat stress, including ERF109, ERF88, DREB1D, ERF25, ERF57, ERF4, and ERF99 (Balfagón et al., 2019a).

Integration of stress signaling during abiotic–biotic interactions

Recent studies are also beginning to unravel molecular regulators mediating the integration of biotic and abiotic signaling pathways during stress combinations. For example, the receptor-like kinase THESEUS1 (THE1) senses

changes in cell wall integrity and link these changes to defense response activation. In addition to its role in defense responses, THE1 is also involved in controlling root growth under salt stress (Liu et al., 2021; Saijo and Loo, 2020), highlighting the possibility that this RLK could mediate the integration of different abiotic and biotic stresses. Another RLK with potential roles in both abiotic and biotic signaling is LysM. LysM plays a key role in defense response activation triggered by the exogenous application of chitin. Interestingly, LysM is also involved in salinity responses in Arabidopsis (Brotman et al., 2012). In addition to RLKs, some MAPK cascades play overlapping roles in biotic and abiotic stresses and could have opposite signaling effects. For example, MPK3/6 and MPK4 cascades antagonize each other during cold stress and immune signaling. MPK3/6 attenuates freezing tolerance, while MPK4 positively regulates it. In contrast, MPK3/6 positively regulate immunity, while MPK4 negatively regulates it (reviewed in Saijo and Loo, 2020). Many biotic and abiotic stresses activate apoplastic ROS production via the activation of respiratory burst NADPH oxidase (RBOH) proteins, and this signaling process plays an important role in the triggering of local and systemic responses to stress (Choi et al., 2017; Gilroy et al., 2016; Suzuki et al., 2011; Zandalinas et al., 2020a). Stresses that trigger RBOH-driven ROS production include biotic stresses such as aphid, bacteria, or fungal infestation (Jaouannet et al., 2015; Lee et al., 2020; Qi et al., 2017), as well as abiotic stresses such as salinity, heat, mechanical injury, or high light stress (Jiang et al., 2012; Miller et al., 2009; Zandalinas et al., 2020a,b; Zandalinas and Mittler, 2021). Because RBOHs such as the AtRBOHD are regulated through multiple post-translational mechanisms by different biotic and/or abiotic stresses (e.g., calcium binding, phosphorylation, dephosphorylation, S-nitrosylation, and/or ubiquitination; Fichman and Mittler, 2020; Kadota et al., 2014, 2015), during stress combinations they could function as a central integration hub for different signals. Two different stresses could, for example, result in the activation of RBOHs via different post-translational mechanisms resulting in the production of different stress-specific ROS signatures that differ in their intensity, time of activation, and/or duration. However, when the two stresses are combined, the two different pathways causing each a stress-specific activation of RBOHs would integrate via combined post-translational modifications of RBOH resulting in an altered, or an even completely new, ROS signature that could be specific for the stress combination (Choudhury et al., 2017).

In addition, and similar to the integration of different abiotic stresses described above, different abiotic and biotic stresses trigger the accumulation of specific members of TF families, including heat shock factor, WRKY, MYB, AP2/ERF, NAC, bZIP, and TCP (Fujita et al., 2010). For example, the transcriptional regulator ERF1 controls ethylene

responses to pathogen attack in Arabidopsis, as well as plays a positive role in salt, drought, and heat stress tolerance integrating JA, ET, and ABA signaling (Berrocal-Lobo et al., 2002). Another molecular integration point for abiotic (i.e., cold stress) and biotic (i.e., bacterial pathogens) are the Calmodulin-binding Transcription Activator (CAMTA) TFs. CAMTA1, CAMTA2, and CAMTA3 serve as master regulators of SA-mediated immunity, repressing the biosynthesis of SA in healthy plants and regulating pipecolic acid biosynthesis (Kim et al., 2020). Pathogen-induced loss of CAMTA1, CAMTA2, and CAMTA3 repression leads to the induction of plant defense genes and the initiation of systemic acquired resistance. The repression effect of CAMTA TFs over SA biosynthesis can also occur when plants are exposed to cold stress due to a decrease in CAMTA expression (Kim et al., 2017, 2020). Consequently, cold-acclimated plants are more resistant to infection by *Pst* DC3000 than plants growing at moderate temperature (Doherty et al., 2009; Kim et al., 2017). Therefore, CAMTA TFs represent an excellent example for the integration of abiotic and biotic signals. Further research is needed to decipher the mode of abiotic–abiotic and abiotic–biotic interactions during stress combinations, and some of the findings obtained from these studies could be utilized for the development of climate-resilient crops.

FUTURE CHALLENGES AND POTENTIAL STRATEGIES TO IMPROVE CROPS RESILIENCE TO CLIMATE CHANGE

Currently, the genetic variability of plants is being explored at the single nucleotide level using GWAS and other methods of genetic mapping and sequencing, coupled with advanced phenotyping techniques. Advances in studying the spatial and temporal regulation of gene expression and metabolic pathways have also greatly increased thanks to the implementation of large-scale sequencing, metabolomics, machine learning software, and CRISPR-Cas technologies. However, the success of these emerging technologies greatly depends on the identification of mechanisms that regulate plant productivity, growth and yield under field conditions, and stress combinations. A fundamental key will be understanding the metabolic, cellular, and developmental pathways utilized by plants to respond to and interact with their dynamic environment, pathogens, and pollinators. New and modified crop varieties and cultivars must have a “balanced” genetic content that will alleviate the losses caused by single, as well as combined environmental stresses, pests and other rapidly changing environmental conditions. Some of the important objectives include increasing photosynthetic efficiency, altering stomatal regulation, creating a balanced and efficient use of nutrients and water, and encouraging interactions of plants with beneficial microorganisms (Figure 4, Table S2). Some of the possible avenues to increase plant productivity and yield in the face of the predicted

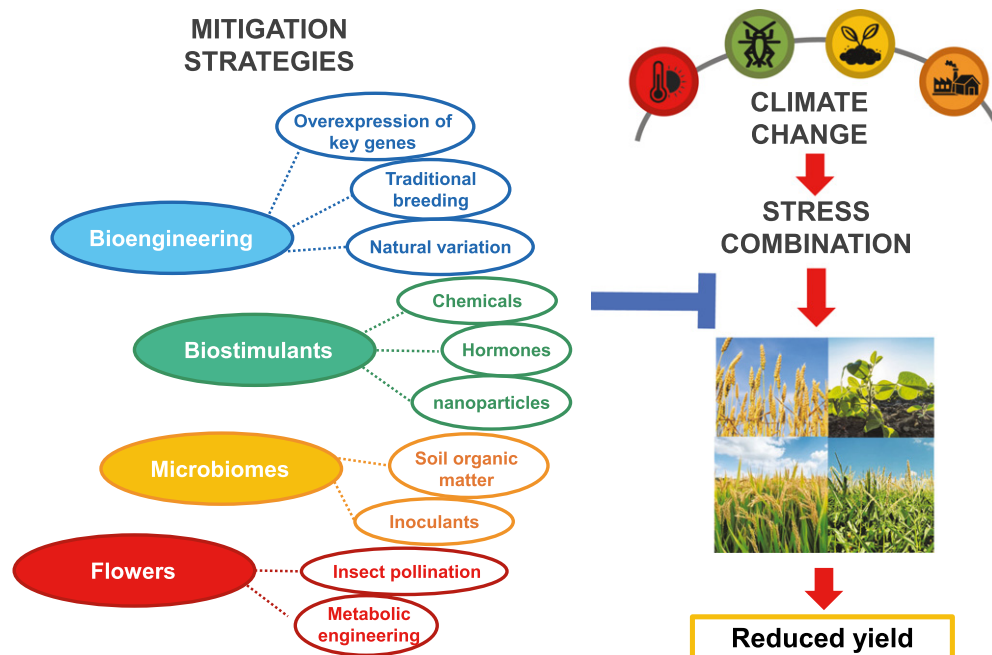


Figure 4. Proposed strategies for the development of climate-resilient crops. Strategies include: bioengineering plants (e.g., overexpressing key genes involved in abiotic stress tolerance); applying biostimulants including chemicals, hormones, or nanoparticles; modifying the plant microbiome (e.g., using inoculants); and improving flower performance by metabolic engineering or increasing flora visitation by pollinators. See also Table S2.

harsh environmental conditions caused by climate change include, among others:

- i Enhancing tolerance to stress combinations with special attention to different climate scenarios that include the simultaneous exposure of crops to heat combined with drought, salinity, flooding, high CO₂ levels, and/or pathogen attack. This task will require better understanding of the specific physiological, metabolic, and signaling mechanisms involved in crop responses to these stress combinations, as well as understanding the positive and negative interactions between different stresses. Continuous cooperation and open interdisciplinary crosstalk among different researchers will be mandatory for successfully achieving this ambitious goal.
- ii Increasing WUE and NUE, through root, stomata, vascular tissue, and biochemical and regulatory engineering, as well as through enhancing plant–microbiome interactions at the rhizosphere, endosphere, and phyllosphere. In this respect, genome-wide studies of crops and microbiomes, coupled with a deep metabolomic analysis and imaging, would be essential.
- iii Improving plant reproduction and seed filling processes under conditions of stress combination. This goal could be achieved by improving the heat and desiccation tolerance of flowers and by improving allocation of photoassimilates from leaves to flowers. Special emphasis should be given to scenarios of

stress combinations that include heat stress, as heat was found to have a severe effect on flowering and reproduction.

- iv Optimizing photosynthetic efficiency by altering the abundance of photosynthetic proteins and minimizing photorespiration, contributing to the enhancement of photosynthetic light efficiency and CO₂ assimilation. Additional targets for this goal include, manipulating stomatal density and stomatal aperture control mechanisms, and optimizing light capture by a wider proportion of the plant canopy.
- v Use synthetic biology, nanoparticle technology, chemistry, and advanced artificial intelligence to develop and introduce novel defense and acclimation strategies, currently not present in crop genomes, into our toolbox of means to mitigate climate change.
- vi Develop, introduce, and improve the use of precision agriculture practices that will enable farmers to mitigate specific aspects of climate change in real time in the field. Included in this goal are improved imaging and mapping technologies, improved robotics and drone technologies, and the development of new chemical application and irrigation methods.

The development of these future technologies will require more active collaboration between different researchers and institutes worldwide, including ecologists, plant biochemists, molecular biologists and physiologists, breeders, chemists, evolutionary biologists, engineers,

computer scientists, bioinformaticians, and many other disciplines. The road ahead is long and challenging, but “climate time” is upon us.

ACKNOWLEDGEMENTS

This work was supported by funding from the National Science Foundation (IOS-2110017, IOS-1353886, MCB-1936590, IOS-1932639), the University of Missouri, Plan GenT 2020 from Generalitat Valenciana (CDEIGENT/2020/013), and the Ministry of Economy and Competitiveness from Spain (grant no. PGC2018-09573-B-100). We apologize to all authors of papers not mentioned in this manuscript due to space limitations.

AUTHOR CONTRIBUTIONS

RMR, EB, RM, and SIZ wrote the manuscript and designed the figures.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

All relevant data can be found within the manuscript.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Environmental and socio-economic impacts of global warming and climate change.

Table S2. Proposed strategies for the development of climate resilient crops.

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