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

Rosa M Rivero^{1,#}, Ron Mittler^{2,#,*}, Eduardo Blumwald³ and Sara I Zandalinas^{2,4,*}

¹Department of Plant Nutrition, Campus Universitario de Espinardo, CEBAS-CSIC, Ed 25, Espinardo, 30100 Murcia, Spain.

²Division of Plant Sciences and Interdisciplinary Plant Group, College of Agriculture, Food and Natural Resources, Christopher S. Bond Life Sciences Center, University of Missouri, 1201 Rollins Street, Columbia, MO 65201, USA.

³Department of Plant Sciences, University of California, 1 Shields Avenue, Davis, CA, 95616, USA

⁴Departamento de Ciencias Agrarias y del Medio Natural, Universitat Jaume I, Av. de Vicent Sos Baynat, s/n, Castelló de la Plana, 12071, Spain

#These authors contributed equally.

*Corresponding authors: izquierdozandalins@missouri.edu; mittlerr@missouri.edu

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Abbreviations: ABA, abscisic acid; CAMTA, calmodulin-binding transcription activator; GWAS, genome-wide association studies; HSF, heat shock factor; HSP, heat shock protein; JA, jasmonic acid; NUE, nitrogen use efficiency; PGPR, plant-growth promoting rhizobacteria; QTLs, Quantitative trait loci; ROS, reactive oxygen species; SA, salicylic acid; TF, transcription factor; WUE, water use efficiency.

Key words: Climate change, global warming, abiotic stress, biotic stress, stress combination, multifactorial stress combination, acclimation strategies, crop plants, yield.

29 **Abstract**

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

49 **Significant statement**

50 Climate change and global warming increase the likelihood that trees and crop plants will be
51 subjected to a combination of different abiotic and biotic stresses, compromising global food
52 production and security. This paper reviews recent advances in the study of plant responses to
53 stress combination and proposes potential strategies to develop crops with high resilience to a wide
54 range of stress factors and their combination.

56 Introduction

57 The constant increase in the accumulation of greenhouse gases, in particular CO₂, has driven a
58 dangerous rise in global land surface and ocean temperatures, termed global warming. This process
59 is causing an increase in the frequency and intensity of drought episodes, heat waves, cold snaps,
60 and flooding, termed climate change (Steg, 2018; Raymond *et al.*, 2020; Anderegg *et al.*, 2020;
61 Hassani *et al.*, 2020; Zandalinas *et al.*, 2021a; Gathen *et al.*, 2021; Houtan *et al.*, 2021; IPCC 2014;
62 Figure 1). Although climate change is thought of as a global phenomenon, its manifestation as
63 changes in short- or long-term weather trends, are different at different regions around the globe
64 and could result in the simultaneous occurrence of two or more different abiotic stress conditions
65 (Figure 1a). For example, in the last several years large areas of the US West were subjected to
66 extreme drought stress combined with heat waves, while many areas of the US Midwest were
67 subjected to flooding and high temperatures. In contrast, many areas in Australia and Northern
68 Africa were subjected to drought, high salinity and high temperatures (Figure 1a;
69 www.climate.gov, NOAA; IPCC 2014; National Drought Mitigation Center;
70 www.droughtmonitor.unl.edu/). These regional climate conditions are frequently combined with
71 harsh soil conditions, including nutrient deficiency, soil salinity, extreme pH, and high levels of
72 different environmental pollutants (*e.g.*, heavy metals, microplastics, herbicides, pesticides,
73 antibiotics and persistent organic pollutants; Zandalinas *et al.*, 2021a; Figure 1b). In addition, many
74 pathogen and pest outbreaks have been linked to changes in climate trends, such as increases in
75 the frequency and intensity of drought episodes, heat waves or flooding events (Hódar *et al.*, 2012;
76 Jactel *et al.*, 2019; Phophi *et al.*, 2020; Salih *et al.*, 2020; Markham and Greenham, 2021). While
77 each of the different abiotic or biotic stresses described above could cause a serious threat to
78 agricultural production, the possible combinations of different stresses occurring as a result of the
79 multifactorial nature of climate change could pose an even greater threat to major crops, global
80 food production, and food security (Figure 1; Table S1; Lobell and Gourdjji, 2012; Liess *et al.*,
81 2016; Alkorta *et al.*, 2017; Suseela and Tharayil, 2018; Rillig *et al.*, 2019a; Jarsjö *et al.*, 2020;
82 Zandalinas *et al.*, 2021a). A recent study suggested for example that the global production of ten
83 major crops including barley, cassava, maize, oil palm, rapeseed, rice, sorghum, soybean,
84 sugarcane and wheat, has already been affected by climate change, and although variability among
85 crops and regions occur, overall consumable food calories of these ten crops has been reduced by
86 about 1% (Ray *et al.*, 2019).

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3 87 Because climate change is likely to increase the exposure of many different crops and trees to
4 88 conditions of stress combination (Figure 1), it is important to understand how different stresses
5 89 interact and affect plant growth, yield and survival. To date, many studies have focused on plant
6 90 responses to a single abiotic or biotic stressor, or to simple stress combinations of two or at the
7 91 most three different stress conditions (*e.g.*, water-deficit stress and heat, salinity and heat, water-
8 92 deficit stress and salinity). These studies revealed that the plant response to a given stress
9 93 combination is often unique, and could not be predicted from the plant response to each of the
10 94 different stress conditions applied individually (*e.g.*, Rizhsky *et al.*, 2002, 2004; Mittler, 2006;
11 95 Mittler and Blumwald, 2010; Prasch and Sonnewald, 2013; Suzuki *et al.*, 2014; Shaar-Moshe *et*
12 96 *al.*, 2017, 2019; Zhang and Sonnewald, 2017; Balfagón *et al.*, 2019a; Zandalinas *et al.*, 2020a). As
13 97 a result, predicting the effects of climate change, that simultaneously impacts many different
14 98 environmental conditions (Figure 1) and could result in conditions of stress combination, on plant
15 99 growth and development, plant reproduction, and the interactions of plants with other organisms
16 100 (including the soil microbiome), is likely to be challenging. It is therefore important to focus
17 101 current and future research efforts on the study of plant responses to stress combination, as well as
18 102 to increase the proportion of stress studies conducted with plants growing in the field and subjected
19 103 to stress combination. Unraveling the complexities of plant responses to stress combination could
20 104 therefore facilitate the development of climate-resilient crops, improving global food production
21 105 and securing our future food supply. Here, we highlight the importance of studying stress
22 106 combination in plants, propose different methods to develop plants with enhanced tolerance to
23 107 stress combination and climate change, and discuss different physiological and molecular
24 108 mechanisms involved in the acclimation of plants to the complex and multifactorial nature of
25 109 climate change.

110 **Physiological and metabolic effects of stress combination on plants**

111 Stress causes a disruption in plant homeostasis impacting key metabolic and physiological
112 processes, limiting energy production, and endangering cellular integrity. To counter the effects
113 of stress, plants must rapidly adjust their metabolic and physiological responses and create a new
114 state of homeostasis in a process termed acclimation (*e.g.*, Walters, 2005). Over longer periods of
115 time, plants may also alter their anatomy and/or growth and reproduction strategies in a process
116 termed adaptation (Bohnert *et al.*, 1995). Because different stresses may impact plants differently,

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3 117 the acclimation or adaptation responses of plants to each different stress condition might require a
4
5 118 different strategy. For example, during drought plants close their stomata to prevent water loss
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7 119 (Nilson and Assmann, 2007; Sun *et al.*, 2014; Hsu *et al.*, 2021), but during heat plants open their
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9 120 stomata to enhance transpiration and cool their leaves (Figure 2a; Zhou *et al.*, 2015; Zandalinas *et*
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11 121 *al.*, 2016a, 2020a). Each different stress might therefore induce in plants a different acclimation
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13 122 and/or adaptation response, and these could have shared or different components. The main
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15 123 problem plants face during stress combination is that the two different stresses simultaneously
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17 124 impacting the plant could require different and sometimes opposing physiological and metabolic
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19 125 responses. Using the example of drought and heat stresses, when combined, these two different
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21 126 stresses require opposing stomatal responses. Under conditions of stress combination, the plant
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23 127 might therefore prioritize one acclimation/adaptation strategy over the other, use a blend of the
24
25 128 two responses, and/or use a completely new strategy. The exact choice of which
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27 129 acclimation/adaptation strategy to use during stress combination is likely to be impacted by the
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29 130 intensity of each individual stress affecting the plant (*i.e.*, which stress level is stronger), as well
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31 131 as by the timing in which they impact the plant (*i.e.*, which stress was first to affect). In the past
32
33 132 several years researchers have begun to dissect the physiological and metabolic responses of
34
35 133 plants to stress combination. Below we will review some of these studies.

34 134 ***Photosynthesis under abiotic stress combination***

36 135 Photosynthesis is highly susceptible to stress combination, with several studies demonstrating that
37
38 136 photosynthetic efficiency and transpiration rates decrease under conditions of water-deficit, salt,
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40 137 and/or heat stresses occurring together (Zlatev and Lidon, 2012; Zandalinas *et al.*, 2016a,b;
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42 138 Perdomo *et al.*, 2017). A combination of drought and heat for example causes a severe reduction
43
44 139 in photosynthetic activity (higher than the effects of drought or heat applied alone). This additive
45
46 140 effect was demonstrated for Arabidopsis (Rizhsky *et al.*, 2004; Zandalinas *et al.*, 2016a), tobacco
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48 141 (Rizhsky *et al.*, 2002), soybean (Jumrani and Bhatia, 2019; Cohen *et al.*, 2021a), lentil (*Lens*
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50 142 *culinaris medikus*) (Sehgal *et al.*, 2017), chickpea (Awasthi *et al.*, 2014), tomato (Zhou *et al.*,
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52 143 2017), maize (Hussain *et al.*, 2019), wheat (Perdomo *et al.*, 2015), and the perennial grass *Leymus*
53
54 144 *chinensis* (Xu and Zhou, 2006). It is thought that this effect results from a combination of two
55
56 145 different processes: *i*) a decrease in carbon assimilation rates, due to stomatal closure, and *ii*) the
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58 146 negative effects of high temperature on PSII integrity (Chen *et al.*, 2018; Li *et al.*, 2020; Gupta *et*
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2
3 147 *al.*, 2021). In addition, it was proposed that a combination of drought and heat stress causes a
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5 148 specific decrease in the steady-state level and functionality of different DNA–protein
6
7 149 conglomerates called chloroplast nucleoids (Shaar-Moshe *et al.*, 2017). In contrast to the additive
8
9 150 negative effects of drought and heat stress combination on photosynthesis, during a combination
10
11 151 of salt and heat stress tomato plants prioritize heat stress responses over salinity responses
12
13 152 (Colmenero-Flores and Rosales, 2014; Rivero *et al.*, 2014). The effects of salinity and heat
14
15 153 combination on photosynthesis is therefore similar to the effect of heat alone, and the opening of
16
17 154 stomata during this stress combination (a heat-driven response) allowed plants to increase CO₂
18
19 155 assimilation rates and improved the overall response of plants to the stress combination. In the last
20
21 156 several years, different breeding and engineering avenues for the improvement of photosynthetic
22
23 157 efficiency in crops growing under field conditions were proposed (Ambavaram *et al.*, 2014;
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25 158 Kromdijk *et al.*, 2016; Rooijen *et al.*, 2017; Simkin *et al.*, 2019; Batista-Silva *et al.*, 2020; Reynolds
26
27 159 *et al.*, 2021). Because photosynthesis plays such an important role in plants responses to stress
28
29 160 combination, it would be very interesting to find out how these modified crops respond to different
30
31 161 scenarios of stress combinations. In addition, due to the important role stomata play in plant
32
33 162 responses to stress combination, new strategies for altering stomata regulation and number in
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35 163 different crops subjected to stress combination could help alleviate the effects of different complex
36
37 164 environmental conditions on crop yields.

165 ***Stomatal regulation under abiotic stress combination***

166 A combination of abiotic stresses can have different and sometimes opposing effects on stomatal
167 regulation (Rizhsky *et al.*, 2004). During heat stress stomata open to cool leaves via transpiration,
168 but during drought stomata close to prevent water loss. During a combination of drought and heat
169 stress, stomata of different plants remain however closed, suggesting that drought-driven
170 regulation of stomata overcomes heat stress-driven regulation during stress combination (Rizhsky
171 *et al.*, 2004; Carmo-Silva *et al.*, 2012; Zandalinas *et al.*, 2020a,c). In contrast, during a combination
172 of high light and heat, heat stress-driven regulation of stomata (stomata opening) was found to
173 overcome high light-driven stomata regulation (stomata closure), resulting in stomata opening
174 during this stress combination condition (Figure 2a; Balfagón *et al.*, 2019a). These differences in
175 stomatal regulation suggest that different hormones and/or other regulatory processes could
176 interact to prioritize one type of stomatal response over the other during stress combination.

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3 177 Studies of hormonal changes during stress combination involving high temperature and other
4 178 abiotic stresses such as salinity or high light demonstrated that a coordinated hormonal response
5 179 to each specific stress combination is essential to trigger proper stomatal responses and acclimation
6 180 (Balfagón *et al.*, 2020). Despite its canonical role in regulating stomatal closure, during some stress
7 181 combinations, the accumulation of abscisic acid (ABA) does not appear to correlate with stomatal
8 182 closure (Zandalinas *et al.*, 2016b; Balfagón *et al.*, 2019b). A lack of correlation between ABA
9 183 levels and stomatal closure was found for example in citrus plants subjected to the combination of
10 184 heat and salinity (Balfagón *et al.*, 2019b), or in Arabidopsis plants subjected to a combination of
11 185 drought and heat stress (Zandalinas *et al.*, 2016b). It was suggested that other signaling molecules
12 186 could play a role in stomatal responses when salt or drought stress occur at high temperatures
13 187 (Balfagón *et al.*, 2020). These include H₂O₂ and jasmonic acid (JA) (Murata *et al.*, 2015;
14 188 Zandalinas *et al.*, 2016a). Accumulation of JA and JA-Ile occurs for example under a combination
15 189 of salinity and high temperatures in citrus plants (Balfagón *et al.*, 2019b), as well as in Arabidopsis
16 190 plants subjected to the combination of high light intensity and heat stress (Balfagón *et al.*, 2019a).
17 191 In addition, it was proposed that H₂O₂ could be playing a role in regulating stomatal responses
18 192 during a combination of drought and heat stress in Arabidopsis plants (Zandalinas *et al.*, 2016a).
19 193 Co-occurring abiotic stress conditions could therefore trigger the accumulation of different
20 194 hormones and/or other signaling molecules that would modulate specific stomatal responses
21 195 (Figure 2a).

196 ***Water and nutrient use efficiency under abiotic stress combination***

197 Stomata closure during stress is directly linked to a reduction of WUE, which is one of the most
198 important parameters in crop responses to osmotic imbalances. WUE is defined as the amount of
199 carbon assimilated as biomass or grain produced per unit of water used by a crop (Hatfield and
200 Dold, 2019). WUE has been studied as a key target for crop improvement for at least a century
201 (Briggs and Shantz, 1913), since water availability is one of the most important environmental
202 factors limiting crop production (Boyer, 1982). Greater temperatures and atmospheric vapor
203 pressure deficit (VPD) as a result of climate change are expected to cause an increase in water
204 uptake by plants in order maintain growth and reproduction (Grossiord *et al.*, 2017). Initially, an
205 increase in environmental CO₂ concentration could increase WUE since photosynthesis is
206 expected to increase. However, if plants are also exposed to other stresses that may impair stomatal

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3 207 regulation, WUE could decline. WUE is a complex trait that is affected by many different plant
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5 208 parameters, such as photosynthesis, stomatal and mesophyll conductance, and canopy structure
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7 209 (Leakey *et al.*, 2019), which together with the complexity of the field environment makes the
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9 210 artificial improvement of WUE a challenging task. In most of the studies performed in different
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11 211 crops subjected to a combination of different abiotic stresses, *e.g.*, drought and heat (Pandey *et al.*,
12
13 212 2021) and drought and salinity (Ranjbarfordoei *et al.*, 2002), a decrease in WUE due to stomatal
14
15 213 and nonstomatal limitations was observed (Pandey *et al.*, 2021). WUE is also affected by the
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17 214 carboxylation pathway utilized by the plant. C4 plants have higher intrinsic WUE than C3 plants,
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19 215 owing to higher photosynthetic rate and lower stomatal conductance (Taylor *et al.*, 2010). Because
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21 216 WUE is such an important trait that impacts yield under field conditions, breeding for an improved
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23 217 WUE under stress combination could provide an additional avenue for the development of climate-
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25 218 resilient crops. In a recent study for example Lehretz *et al.*, (2021) demonstrated that co-expressing
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27 219 hexokinase 1 from Arabidopsis (AtHXK1) in guard cells and SELF-PRUNING 6A (SP6A) in
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29 220 leaves and stems stimulated tuberization and improved WUE under conditions of drought and heat
30
31 221 stress combination in potato. Nitrogen use efficiency (NUE) is generally defined as the amount of
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33 222 grains produced per unit of available nitrogen in the soil. Because climate-driven events of stress
34
35 223 combinations such as drought and heat, flooding and heat, or drought and salinity are likely to
36
37 224 impact nutrient availability and uptake by crops, studying and improving NUE could be an
38
39 225 additional breeding target for generating climate-resilient crops. In addition to breeding,
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41 226 calibrating the amount of N supplied to plants during stress combination could be critical. For
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43 227 example, in a study performed by Ramezanifar *et al.* (2021), spinach plants grown under a
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45 228 combination of water deficit and salinity were supplemented with different amounts of N (from 0
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47 229 to 200 mg N kg⁻¹ soil). This study showed that after reaching a certain (critical) level of N supply
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49 230 (100 to 150 mg N kg⁻¹ soil), further increases in N inputs did not contribute to an increase in yield
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51 231 of spinach subjected to the stress combination (also observed previously by Ramos *et al.*, 2012).
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53 232 Moreover, WUE and NUE decreased under conditions of water deficit combined with salinity and
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55 233 nutrient deprivation. Further studies and breeding efforts are needed to improve WUE and NUE
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57 234 in crops subjected to different stress combinations if we want to achieve our goal of developing
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59 235 crops with enhanced tolerance to climate change.

236 ***Stress combination in a high CO₂ environment***

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3 237 When considering the effects of climate change on stress combination, photosynthesis, WUE,
4 238 NUE, and other important processes for plant growth and survival, we need to take into
5 239 consideration the increase in atmospheric CO₂ levels that will accompany these stresses. At high
6 240 CO₂ stomata of most plants begin to close, decreasing stomatal conductance and transpiration
7 241 (Zhang *et al.*, 2021). While this response could be beneficial during drought stress increasing
8 242 WUE, it may not be beneficial for plants subjected to heat stress, or heat stress combined with high
9 243 light stress that require stomata to remain open (Balfagón *et al.*, 2019a). Because stomatal
10 244 responses affect photosynthesis, WUE, NUE and many other processes in plants, studying the
11 245 effects of high CO₂ concentrations on plant physiology under conditions of stress combination is
12 246 critical. The co-occurrence of elevated CO₂ and combined drought and heat was studied in
13 247 *Arabidopsis thaliana* (Zinta *et al.*, 2014), *Triticum aestivum* (Fitzgerald *et al.*, 2016), *Brassica*
14 248 *napus* (Dikšaitytė *et al.*, 2019), wheat (Abdelhakim *et al.*, 2021), and the C3 grassland plant
15 249 *Trifolium repens* (Roy *et al.*, 2016). These studies showed that high CO₂ levels alleviate the
16 250 negative impacts of drought and heat combination. The mitigation effect of CO₂ on biomass
17 251 reduction, photosynthesis inhibition, chlorophyll fluorescence decline, ROS production and
18 252 protein oxidation in *Arabidopsis* plants subjected to the combination of water deficit and heat were
19 253 associated with reduced photorespiration and increased content of different antioxidant
20 254 mechanisms (Zinta *et al.*, 2014). High CO₂ was also found to enhance wheat yield in semi-arid
21 255 environments under heat waves (Fitzgerald *et al.*, 2016), improve plant water relations and
22 256 photosynthesis rate at saturating light in *Brassica napus* (Dikšaitytė *et al.*, 2019), increase net
23 257 photosynthetic rates and maintain maximum quantum efficiency of PSII photochemistry in wheat
24 258 (Abdelhakim *et al.*, 2021), as well as mitigate the impact of extreme heat and drought on net carbon
25 259 uptake in the C3 grassland plant *Trifolium repens* (Roy *et al.*, 2016). In contrast, Zhou *et al.*, (2020)
26 260 showed that tomato plants grown at elevated CO₂ concentration were more sensitive to combined
27 261 drought and heat stress than those grown at ambient CO₂ due to a higher decrease in net
28 262 photosynthesis, stomatal conductance and transpiration, leading to an increased severity of the
29 263 water deficit effects. Although in general high CO₂ levels promote vegetative growth due to
30 264 increased CO₂ fixation, altered redox state, reduced photorespiration and improved WUE, the
31 265 effects of high CO₂ concentrations on grain quality, and especially grain protein content could be
32 266 negative if N availability is limited (*e.g.*, Umnajkitikorn *et al.*, 2020). This is another aspect of
33 267 high CO₂ and stress combination that needs to be addressed, especially in light of the potential

268 negative effects of stress combination on NUE. Because the breath of high CO₂ effects on crops is
269 too vast to cover here, the reader is directed to several excellent reviews on the subject (Soh *et al.*,
270 2019; Toreti *et al.*, 2020; Tausz-Posch *et al.*, 2020; Penuelas *et al.*, 2020; Xu *et al.*, 2020; Green
271 *et al.*, 2020; Lu *et al.*, 2020; Wang *et al.*, 2020; Bright and Lund, 2021; Wang and Liu, 2021;
272 Lamichaney and Maity, 2021; Schmidt *et al.*, 2021; Smith, 2021; Ainsworth and Long, 2021;
273 Delabre *et al.*, 2021; Kurganskiy *et al.*, 2021).

274 **Effect of stress combination on reproductive processes**

275 Sexual plant reproduction requires a complex and highly coordinated set of developmental
276 processes that are tightly regulated and synchronized. Many of these processes, *e.g.*, pollen
277 maturation, fertilization, embryogenesis, and seed maturation are highly sensitive to different
278 abiotic stress conditions such as heat and drought that could lead to pollen, embryo, or seed
279 abortion (Barnabás *et al.*, 2008; Ruan *et al.*, 2010; Prasad *et al.*, 2011, 2015; Awasthi *et al.*, 2014;
280 Lawas *et al.*, 2019; Jiang *et al.*, 2019; Cohen *et al.*, 2021b; Figure 2b). One of the reasons abiotic
281 stresses impair these processes is the production of ROS under conditions of stress. In reproductive
282 tissues, ROS such as superoxide and hydrogen peroxide play an important signaling role in the
283 triggering of different developmental programs such as the programmed cell death of the tapetum
284 layer, the germination of pollen on the surface of the stigma, or the entry of the growing pollen
285 tube tip through the synergid cells into the egg sack (Barnabás *et al.*, 2008; Prasad *et al.*, 2015;
286 Kurusu and Kuchitsu, 2017; Mhamdi and Van Breusegem, 2018). The production of ROS during
287 these developmental processes is highly coordinated, transient, and restricted to specific tissues.
288 Stress, causing the uncontrolled and unsynchronized accumulation of ROS in many different
289 reproductive tissues, could therefore impair these developmental programs and cause a decrease
290 in fertilization rates, embryogenesis, and overall seed production (Figure 2b; Sinha *et al.*, 2021).
291 The remarkable decreases in yield occurring when different crops are subjected to heat, cold, or
292 drought stress during the flowering season (FAO, Food and Agriculture Organization;
293 <https://www.fao.org/>) clearly demonstrate the vulnerability of reproductive processes to abiotic
294 stresses (Barnabás *et al.*, 2008; Prasad *et al.*, 2015). Moreover, as a recent meta-analysis revealed,
295 the decrease in yield of many crops is further increased when different abiotic stresses are
296 combined during plant reproduction (Cohen *et al.*, 2021b). The combination of drought and heat
297 stress for example significantly impacted plant yield by decreasing harvest index (HI), shortening

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2
3 298 the life cycle of crops, and altering seed number, size and composition (Cohen *et al.*, 2021b). A
4
5 299 more dramatic reduction in seed weight was found in cereals compared to legumes, while the
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7 300 negative effect of the stress combination on HI and individual seed weight in legumes was lower
8
9 301 than in cereals (Cohen *et al.*, 2021b). During flowering, pollen is particularly sensitive to high
10
11 302 temperatures, especially when combined with drought (Ruan *et al.*, 2010; Jiang *et al.*, 2019).
12
13 303 Stigma functionality and fertility are also highly sensitive to combined drought and heat in wheat
14
15 304 plants, leading to flower abortion (Fábián *et al.*, 2019). Stress combination also affects the
16
17 305 chemical composition and secretion of nectar potentially affecting plant pollinators interactions
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19 306 (Glenny *et al.*, 2018; Borghi *et al.*, 2019; Figure 2b). Frequent increments in light intensity and
20
21 307 ambient temperature, which often co-occur during drought episodes, exacerbated the incidence of
22
23 308 nectar loss, potentially affecting pollination (Borghi *et al.*, 2019). In addition, it was reported that
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25 309 flora visitation by pollinators was severely compromised when high CO₂ impacted plants together
26
27 310 with drought and heat (Glenny *et al.*, 2018). Different abiotic stress combinations alter the use of
28
29 311 carbohydrates in anthers of many crop and model species (Borghi *et al.*, 2019). For example,
30
31 312 studies in rice suggested that sugar starvation in floral organs was the underlying factor in
32
33 313 reproductive failure in response to the combination of drought and heat (Li *et al.*, 2015; Lawas *et*
34
35 314 *al.*, 2018). Maize kernel abortion was the main reason for the decrease in kernel numbers per spike
36
37 315 due to a combination of drought and heat stress, which resulted from the prevention of sugar–
38
39 316 starch conversion and limited availability of sugars to kernels during this stress combination (Liu
40
41 317 *et al.*, 2020). In rice, while elevated CO₂ had a positive impact at the reproductive and grain filling
42
43 318 stages (higher seed-set and improved sugar partitioning to the sink tissue as well as higher
44
45 319 photosynthetic rate), a combination of elevated CO₂ and high temperatures led to a significant
46
47 320 decline in seed-set and lowered the levels of sink metabolizing enzymes (Chaturvedi *et al.*, 2017).
48
49 321 The examples described above reveal that more research is needed into the effects of stress
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51 322 combination occurring during plant reproduction. Grains, that comprise the majority of our food
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53 323 source, are the direct result of successful reproduction and must be preserved to ensure food
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55 324 security in the face of our changing climate. In addition to sexual plant reproduction, vegetative
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57 325 propagation of different plants could also suffer from climate change because the process of
58
59 326 storage organ formation (*e.g.*, tubers in potato) is highly sensitive to heat stress.

327 **The soil microbiome and stress combination**

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3 328 The soil microbiome and its interactions with plants play a key role in plant development,
4 329 reproduction, and overall health (*e.g.*, plant growth-promoting rhizobacteria; PGPR; Berendsen *et*
5 330 *al.*, 2012; Wei *et al.*, 2019; Figure 2c). In recent years many studies have shown that global
6 331 warming, climate change and the increased levels of pollutants in different soils around the world
7 332 can cause a significant decline in the complexity and composition of the soil microbiome, raising
8 333 the alarming possibility that this decline would also impact agricultural productivity (Sergaki *et*
9 334 *al.*, 2018; Rillig *et al.*, 2019b; Delitte *et al.*, 2021). In addition to the root microbiome, found
10 335 primarily at the plant rhizosphere, plants also harbor microbiomes on their above-ground surfaces
11 336 (*i.e.*, their phyllosphere), or internally between their cells (*i.e.*, their endosphere), and all three
12 337 microbiomes are thought to potentially promote plant growth and enhance resistance to different
13 338 stresses (Figure 2c). The plant microbiome is dynamic, and its structure and function changes
14 339 depending on the surrounding environmental conditions (Timm *et al.*, 2018). These changes are
15 340 thought to be driven by overall changes in the root microenvironment, apoplastic fluid, and cuticle
16 341 properties, as well as by the plant strategy of actively seeking cooperation with specific types of
17 342 microorganisms, especially during conditions of environmental stress (Bakker *et al.*, 2018). This
18 343 active process is mediated through the synthesis and excretion of a wide range of chemicals that
19 344 attract different populations of bacteria (Bakker *et al.*, 2018; Carrión *et al.*, 2019). The resulting
20 345 interactions are then thought to increase plant tolerance to different abiotic stresses (Hassan and
21 346 Mathesius, 2012; Schulz-Bohm *et al.*, 2018; Fitzpatrick *et al.*, 2018; Lombardi *et al.*, 2018;
22 347 Stringlis *et al.*, 2018; Liu and Brettell, 2019). To date, very little is known however about the role
23 348 of plant-microbiome interactions in plant responses to abiotic stress combinations, especially
24 349 under the predicted increase in CO₂ levels (*e.g.*, Tchakounté *et al.*, 2020; Bilal *et al.*, 2020). As
25 350 discussed below, the use of specialized inoculums targeted for different stress combinations and
26 351 specific crops should be explored in more detail to increase our chances of producing climate-
27 352 resilient crops. Because stress combination can negatively impact soil microbiomes (Rocca *et al.*,
28 353 2019; Rillig *et al.*, 2019b; Valliere *et al.*, 2020), care should be taken to match the bacterial/fungal
29 354 inoculum with the harsh conditions facing the plant, and feasibility studies should be conducted
30 355 under field conditions in multiple locations.

356 **Impact of abiotic stress on plant susceptibility to pathogens and pests**

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2
3 357 The mode and outcome of many plant–microbe interactions, including plant disease epidemics,
4 358 are profoundly influenced by abiotic factors, such as light, temperature, water availability and soil
5 359 nutrient levels (Saijo and Loo, 2020). Additional factors impacting such biotic-abiotic interactions
6 360 include the plant genotype, age and developmental stage, pathogen type and infection mode, the
7 361 nature, strength and timing of abiotic stress, and the impact of stress on plant metabolism (*e.g.*,
8 362 sugar levels and sensing; Saijo and Loo, 2020; Littlejohn *et al.*, 2021). For example, Berens *et al.*,
9 363 (2019) reported that biotic and abiotic stress responses are differentially prioritized in *Arabidopsis*
10 364 *thaliana* leaves of different ages to maintain growth and reproduction under combined biotic and
11 365 abiotic stresses. Abiotic stresses, such as high salinity and drought, suppressed immune responses
12 366 in older rosette leaves through ABA signaling, whereas this antagonistic effect was blocked in
13 367 younger rosette leaves by GRETCHEN HAGEN 3.12 (GH3.12), a signaling component of the
14 368 defense phytohormone salicylic acid (SA) (Berens *et al.*, 2019). In general, abiotic stresses
15 369 increase susceptibility to hemibiotrophic or necrotrophic pathogens, including otherwise weakly-
16 370 virulent facultative pathogens, but reduce susceptibility to biotrophic pathogens (Saijo and Loo,
17 371 2020). Many abiotic stress conditions were also shown to alter the transcriptomic response of
18 372 plants to biotic pathogens and enhance susceptibility to infection (Atkinson and Urwin, 2012;
19 373 Suzuki *et al.*, 2014). For example, a transcriptomic analysis of *Arabidopsis* plants subjected to a
20 374 combination of heat, drought and virus infection revealed that the stress combination inhibited the
21 375 expression of transcripts involved in the R-mediated disease response but enhanced the expression
22 376 of transcripts associated with the heat stress response. These results suggested that abiotic stress
23 377 factors could alter pathogen-related signaling networks that in turn could suppress defense
24 378 responses (Prasch and Sonnewald, 2013). The simultaneous impact of water stress and insect
25 379 herbivory was found for example to reduce yield due to improved herbivore performance on water-
26 380 stressed faba beans (Raderschall *et al.*, 2021). In addition, high temperatures were shown to
27 381 increase virulence of pathogens in different plants (Desaint *et al.*, 2020; Cohen and Leach, 2020;
28 382 Zarattini *et al.*, 2021). In rice plants challenged with the fungus *Magnaporthe oryzae*, which causes
29 383 rice blast, faster pathogen proliferation and increased disease symptoms were observed at high
30 384 temperatures (Onaga *et al.*, 2017). In *Arabidopsis*, high temperature reduced the expression of the
31 385 immune receptor FLAGELLIN SENSING 2 (FLS2), which suppresses immunity to the pathogen
32 386 *Pseudomonas syringae* pv. tomato (Janda *et al.*, 2019). Moreover, it was reported that
33 387 simultaneous pathogen and high temperatures exposure could affect not only pathogen resistance

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2
3 388 but also heat tolerance. An example could be the higher susceptibility of tomato plants to *Tomato*
4 389 *yellow leaf curl virus* (TYLCV) when exposed to heat stress and the compromised heat responses
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6 390 of tomato plants infected by TYLCV (Ghandi *et al.*, 2016). In addition to high temperatures, some
7
8 391 studies suggested that drought increased plant susceptibility to pathogen attack (Zarattini *et al.*,
9
10 392 2021). A recent meta-analysis indicated that increased temperatures, CO₂ concentration, drought
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12 393 stress and nutrient deficiency resulted in greater herbivore consumption, primarily in agricultural
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14 394 systems (Hamann *et al.*, 2021). In contrast to the studies described above, certain abiotic stress
15
16 395 conditions enhanced the resistance of plants to biotic stress (Rouhier and Jacquot, 2008). For
17
18 396 example, cold stress was shown to confer increased disease resistance against hemi- and biotrophic
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20 397 pathogens (Zarattini *et al.*, 2021). It was reported that short-term exposure to 4°C positively
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22 398 modulated SA-dependent responses at the expense of the JA pathway in *Arabidopsis* (Wu *et al.*,
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24 400 *syringae* DC3000 in *Arabidopsis* plants (Gupta *et al.*, 2016), and to delay powdery mildew disease
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26 401 development in *Alliaria petiolate* (Pandey *et al.*, 2017). The potential of abiotic conditions to alter
27
28 402 plant–pathogen and plant-insect interactions highlights the complexity associated with attempts to
29
30 403 generate climate-resistant crops. While some strategies may increase tolerance to both abiotic and
31
32 404 biotic stresses, some may increase resistance to abiotic stresses at the cost of enhancing
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34 405 susceptibility to biotic challenges. Further studies are therefore needed to examine the impact of
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36 406 climate change on pathogen and insect populations and diversity, on the general state of plant
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38 407 fitness, and on the different interactions of plants with different pathogens and pests.

39 408 **Molecular and regulatory responses of plants to stress combinations**

40 409 *Integration of molecular responses during stress combinations*

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45 410 The co-occurrence of different stresses could result in the activation of conflicting, additive, or
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47 411 completely unrelated molecular responses due to the triggering of different stress-response
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49 412 sensors, signaling cascades, and regulatory networks. In addition, the synthesis of different, and
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51 413 sometimes antagonistic hormones (for example JA and SA; Takahashi *et al.*, 2004; Li *et al.*, 2019;
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53 414 Yang *et al.*, 2019), may simultaneously increase during stress combination, leading to conflicting
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55 415 molecular responses. Because different stresses may require different acclimation strategies, plants
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57 416 may prioritize one type of response over the other or use a blend of different molecular and

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3 417 acclimation strategies (Pandey *et al.*, 2015; Liess *et al.*, 2016; He *et al.*, 2018; Zandalinas *et al.*,
4 418 2018; Gull *et al.*, 2019). These types of strategies are often revealed by transcriptomics or genome-
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6 419 wide association studies (GWAS) of plants subjected to stress combination that identifies both
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8 420 common and unique responses.
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11 421 Common signaling pathways and genes that function during different stress combinations as well
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13 422 as during single stresses have been previously described (Rizhsky *et al.*, 2004; Pandey *et al.*, 2015;
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15 423 Shaar-Moshe *et al.*, 2017, 2019; Zandalinas *et al.*, 2021b,a). Such pathways and genes could be
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17 424 associated with universal stress responses, or represent cross-talk between signaling pathways
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19 425 (Prasch and Sonnewald, 2015). For example, 29 transcripts were commonly upregulated in
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21 426 response to drought, heat, and their combination in Arabidopsis plants. These included different
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23 427 heat shock proteins (HSPs) and transcripts related to ABA and ethylene signaling (Rizhsky *et al.*,
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25 428 2004). A large overlap between transcript responses was also found in wheat during a combination
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27 429 of drought and heat stress (Liu *et al.*, 2015). In addition, G-BOX BINDING FACTOR3 (GBF3)
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29 430 was expressed during single and all combined stress conditions of drought, heat and virus (Prasch
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31 431 and Sonnewald, 2013), as well as during individual and combined heat, salt, and osmotic stresses
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33 432 (Sewelam *et al.*, 2014), indicating that GBF3 could be involved in general stress responses. More
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35 433 recently, a transcriptomic study of Arabidopsis plants subjected to a multifactorial stress
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37 434 combination of high light, heat stress, cadmium, acidity, paraquat and salt (Figure 3), revealed that
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39 435 the steady-state level of 136 and 127 transcripts was significantly enhanced or suppressed,
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41 436 respectively, in response to all different stress combinations studied. Some of the upregulated
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43 437 transcripts in this group were involved in the regulation of transcription, redox control, stress
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45 438 responses and ABA responses, whereas some of the downregulated transcripts included were
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47 439 involved in amino acid and carbohydrate metabolism, heme-binding and glutathione transferase
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49 440 and peroxidase activities (Zandalinas *et al.*, 2021b,a).

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51 441 In addition to common responses to individual and combined stresses, several transcriptomic
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53 442 studies of plants subjected to different stresses and their combinations identified unique responses
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55 443 specific to stress combination. For example, a combination of drought and heat altered the
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57 444 expression of over 770 transcripts that were not altered by drought or heat stress (Rizhsky *et al.*,
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59 445 2004). A transcriptomic study of Arabidopsis plants subjected to drought, heat stress, virus
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446 infection and double or triple combinations of these stresses revealed that many transcripts were

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3 447 specifically upregulated only under the combination of all three stresses (Prasch and Sonnewald,
4 448 2013). Other examples include transcriptome studies of drought and O₃ combination (Iyer *et al.*,
5 449 2013), and high light and heat combinations (Balfagón *et al.*, 2019a). Interestingly, the
6 450 transcriptomics study of Zandalinas *et al.*, (2021b) that focused on different multifactorial stress
7 451 combinations (Figure 3) identified different stress-response pathways activated in response to many
8 452 individual abiotic stresses and some of their simple two-stress combinations, but not by specific
9 453 sets of three or four-stress combinations. These, included classical stress-response pathways such
10 454 as heat shock factors (HSFs), the unfolded protein response (UPR), autophagy, and osmoregulation
11 455 (Zandalinas *et al.*, 2021b). It was proposed that the function of some of these could be replaced by
12 456 yet unknown pathways, since the same specific sets of three or four-stress combinations resulted in
13 457 the enhanced expression of large numbers of transcripts with unknown function.
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23 458 Quantitative trait loci (QTL) uniquely associated with stress combinations could be identified by
24 459 GWAS studies. A comprehensive study of the response of 350 different *Arabidopsis* accessions to
25 460 15 different single abiotic and biotic stresses and some of their two abiotic-biotic stress
26 461 combinations reported cross-correlations between specific SNPs and responses to osmotic stress or
27 462 drought combined with root-knot nematodes (Thoen *et al.*, 2017). Another GWAS study using a
28 463 collection of 300 tropical and subtropical maize inbred lines identified genetic markers for grain
29 464 yield and flowering time under a combination of drought and heat stress (Yuan *et al.*, 2019). In
30 465 addition, maize lines with high levels of tolerance to combined drought and heat stress were found
31 466 in a study conducted using 300 maize inbred lines (Cairns *et al.*, 2013). In this study, tolerance to
32 467 a combination of drought and heat was associated with genetic markers that were different from
33 468 those associated with tolerance to individual stresses. Furthermore, in a screen of a tomato
34 469 introgression line population of 31 lines subjected to a combination of salinity and powdery mildew,
35 470 a negative impact of salinity on powdery mildew resistance was identified (Kissoudis *et al.*, 2015).
36 471 Davila Olivas *et al.*, (2017) used a collection of 350 *Arabidopsis* accessions to explore the natural
37 472 variation underlying tolerance to different combinations of abiotic and biotic stresses. This study
38 473 revealed that the number of significant SNPs identified in response to stress combination was
39 474 greater than that in responses to single stresses and identified a list of candidate genes associated
40 475 with combined drought and herbivore stress.
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55 476 ***Integration of stress signaling during abiotic stress combinations***

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3 477 Many different signal transduction mechanisms are involved in stress sensing and signaling in
4 478 plants. These include different stress-specific sensors/receptor molecules, a large network of
5 479 calcium channels and pumps that generate different stress-specific calcium oscillation signatures,
6 480 various ROS sensors, scavengers and producers that generate different ROS signatures across the
7 481 different cellular compartments, and multiple networks of kinases and phosphatases that decode
8 482 the different signals generated and trigger different and sometimes integrated networks of
9 483 transcriptional regulators/factors (Knight and Knight, 2001; Prasad and Sonnewald, 2015; Zhu,
10 484 2016; Raja *et al.*, 2017; Mohanta *et al.*, 2018; Overmyer *et al.*, 2018). Many of these stress
11 485 signaling-associated proteins, enzymes and channels are further thought to co-localize (*e.g.*, as
12 486 parts of lipid rafts and/or protein complexes), creating signalosomes that could also be stress-
13 487 specific (Gilroy and Trewavas, 2001; Dietz *et al.*, 2010). Adding to this complex signaling
14 488 environment is the fact that many different stress-sensing and signaling events occur in different
15 489 organelles and involve a complex mode of communication between different organelles and the
16 490 nuclei (*e.g.*, anterograde and retrograde; Jiang and Dehesh, 2021), and that many other signaling
17 491 molecules, hormones and processes, such as S-nitrosylation, ubiquitination, and myristylation are
18 492 involved in controlling these processes (Stulemeijer and Joosten, 2008; Martínez-Ruiz *et al.*,
19 493 2013). Keeping this high level of complexity in mind, it is not surprising that not much is known
20 494 about how different stress-specific signals (*e.g.*, drought-, heat-, or pathogen-specific signals) are
21 495 integrated when two or more stresses are impacting the plant simultaneously (*i.e.*, during stress
22 496 combination).

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39 497 In recent years some examples for the integration of different stress signaling pathways during
40 498 stress combination were reported. These include different members of several transcription factor
41 499 (TF) families. For example, certain MYB TFs were found to be specific for a combination of
42 500 drought and heat stress in Arabidopsis plants (Rizhsky *et al.*, 2004). Analysis of the regulation of
43 501 different MYB TFs in response to a combination heat and salt, heat and drought, and heat and high
44 502 light in Arabidopsis plants revealed that the expression of MYBs 7 and 32 was enhanced and the
45 503 expression of MYBs 30 and 51 was suppressed, during stress combinations (Zandalinas *et al.*,
46 504 2020c). In addition to MYBs, members of the WRKY TF family were reported to respond to several
47 505 different stress combinations. For example, AtWRKY40 acts antagonistically to AtWRKY18 and
48 506 AtWRKY60 to enhance Arabidopsis tolerance to salt and osmotic stress via ABA signaling (Chen

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3 507 *et al.*, 2010). In addition, 5 WRKY family members (WRKYs 50, 53, 42, and 65, and the
4
5 508 calmodulin-binding WRKY7 repressor) were found to be expressed in response to combined ozone
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7 509 and drought stress in *Medicago truncatula* plants, suggesting that WRKYs could play a role during
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9 510 this stress combination (Iyer *et al.*, 2013). Another TF family with important roles in plant stress
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11 511 responses is the AP2/ERF family. Within this TF family, DREBs were found to positively regulate
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13 512 cold, drought, heat and salt tolerance, as well as different stress combinations by regulating different
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15 513 stress-responsive genes (Maruyama *et al.*, 2009; Xie *et al.*, 2019; Zandalinas *et al.*, 2020c). DREB2
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17 514 TFs are for example induced upon drought and heat, and positively regulate stress-response genes
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19 515 such as LEAs and chaperons (Maruyama *et al.*, 2009), whereas members of DREB-A4 family such
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21 516 as HARDY (HRD) and DREB-A6 family such as ERF53, RAP2.4 and RAP2.4A, positively
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23 517 regulate plant responses to drought and salinity (reviewed in Xie *et al.*, 2019). In addition, different
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25 518 ERF subfamilies including ERF-VI, ERF-VII, ERF-XI and ERF-X have emerged as central players
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27 519 in plant responses to different plant hormones (*e.g.*, ethylene and ABA), metabolic changes, and
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29 520 abiotic stresses in Arabidopsis including flooding, cold, drought, salinity and heat (Xie *et al.*, 2019).
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31 521 In addition, several AP2/ERF TFs are specifically upregulated in Arabidopsis in response to a
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33 522 combination of high light and heat stress, including ERF109, ERF88, DREB1D, ERF25, ERF57,
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35 523 ERF4, and ERF99 (Balfagón *et al.*, 2019a).

524 ***Integration of stress signaling during abiotic-biotic interactions***

36 525 Recent studies are also beginning to unravel molecular regulators mediating the integration of
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38 526 biotic and abiotic signaling pathways during stress combination. For example, the receptor-like
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40 527 kinase THESEUS1 (THE1) senses changes in cell wall integrity and link these changes to defense
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42 528 response activation. In addition to its role in defense responses, THE1 is also involved in
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44 529 controlling root growth under salt stress (Saijo and Loo, 2020; Liu *et al.*, 2021), highlighting the
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46 530 possibility that this RLK could mediate the integration of different abiotic and biotic stresses.
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48 531 Another RLK with potential roles in both abiotic and biotic signaling is LysM. LysM plays a key
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50 532 role in defense response activation triggered by the exogenous application of chitin. Interestingly,
51
52 533 LysM is also involved in salinity responses in Arabidopsis (Brotman *et al.*, 2012). In addition to
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54 534 RLKs, some MAPK cascades play overlapping roles in biotic and abiotic stresses and could have
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56 535 opposite signaling effects. For example, MPK3/6 and MPK4 cascades antagonize each other
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58 536 during cold stress and immune signaling. MPK3/6 attenuates freezing tolerance, while MPK4

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2
3 537 positively regulate it. In contrast, MPK3/6 positively regulate immunity, while MPK4 negatively
4 538 regulate it (reviewed in Saijo and Loo, 2020). Many biotic and abiotic stresses activate apoplastic
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6 539 ROS production via the activation of respiratory burst NADPH oxidases (RBOHs) proteins, and
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8 540 this signaling process plays an important role in the triggering of local and systemic responses to
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10 541 stress (Suzuki *et al.*, 2011; Gilroy *et al.*, 2016; Choi *et al.*, 2017; Zandalinas *et al.*, 2020a). Stresses
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12 542 that trigger RBOH-driven ROS production include biotic stresses such as aphid, bacteria, or fungal
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14 543 infestation (Jaouannet *et al.*, 2015; Qi *et al.*, 2017; Lee *et al.*, 2020), as well as abiotic stresses such
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16 544 as salinity, heat, mechanical injury, or high light stress (Miller *et al.*, 2009; Jiang *et al.*, 2012;
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18 545 Zandalinas *et al.*, 2020a,b; Zandalinas and Mittler, 2021). Because RBOHs such as the AtRBOHD
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20 546 are regulated through multiple post-translational mechanisms by different biotic and/or abiotic
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22 547 stresses (*e.g.*, calcium binding, phosphorylation, dephosphorylation, S-nitrosylation, and/or
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24 548 ubiquitination; Kadota *et al.*, 2014, 2015; Fichman and Mittler, 2020), during stress combination
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26 549 they could function as a central integration hub for different signals. Two different stresses could
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28 550 for example result in the activation of RBOHs via different post-translational mechanisms
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30 551 resulting in the production of different stress-specific ROS signatures that differ in their intensity,
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32 552 time of activation, and/or duration. However, when the two stresses are combined, the two
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34 553 different pathways causing each a stress-specific activation of RBOHs would integrate via a
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36 554 combined post-translational modifications of RBOH resulting in an altered, or an even completely
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38 555 new, ROS signature that could be specific for the stress combination (Choudhury *et al.*, 2017).

37 556 In addition, and similar to the integration of different abiotic stresses described above, different
38
39 557 abiotic and biotic stresses trigger the accumulation of specific members of TF families, including
40
41 558 HSF, WRKY, MYB, AP2/ERF, NAC, bZIP and TCP (Fujita *et al.*, 2010). For example, the
42
43 559 transcriptional regulator ERF1 controls ethylene responses to pathogen attack in *Arabidopsis*, as
44
45 560 well as plays a positive role in salt, drought, and heat stress tolerance integrating JA, ET, and ABA
46
47 561 signaling (Berrocal-Lobo *et al.*, 2002). Another molecular integration point for abiotic (*i.e.*, cold
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49 562 stress) and biotic (*i.e.*, bacterial pathogens) are the Calmodulin-binding Transcription Activator
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51 563 (CAMTA) TFs. CAMTA1, CAMTA2 and CAMTA3 serve as master regulators of SA-mediated
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53 564 immunity, repressing the biosynthesis of SA in healthy plants and regulating pipecolic acid
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55 565 biosynthesis (Kim *et al.*, 2020). Pathogen-induced loss of CAMTA1, CAMTA2 and CAMTA3
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57 566 repression leads to the induction of plant defense genes and the initiation of SAR. The repression

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3 567 effect of CAMTA TFs over SA biosynthesis can also occur when plants are exposed to cold stress
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5 568 due to a decrease in CAMTA expression (Kim *et al.*, 2017, 2020). As a result, cold-acclimated
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7 569 plants are more resistant to infection by *Pst* DC3000 than plants growing at moderate temperature
8
9 570 (Doherty *et al.*, 2009; Kim *et al.*, 2017). CAMTA TFs represent therefore an excellent example
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11 571 for the integration of abiotic and biotic signals. Further research is of course needed to decipher
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13 572 the mode of abiotic-abiotic and abiotic-biotic interactions during stress combination, and some of
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15 573 the findings obtained from these studies could be utilized for the development of climate-resilient
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17 574 crops.

18 575 **Future challenges and potential strategies to improve crops resilience to climate** 19 20 576 **change**

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23 577 Currently, the genetic variability of plants is being explored at the single nucleotide level using
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25 578 GWAS and other methods of genetic mapping and sequencing, coupled with advanced
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27 579 phenotyping techniques. Advances in studying the spatial and temporal regulation of gene
28
29 580 expression and metabolic pathways have also greatly increased thanks to the implementation of
30
31 581 large-scale sequencing, metabolomics, machine learning software, and CRISPR-Cas technologies.
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33 582 However, the success of these emerging technologies greatly depends on the identification of
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35 583 mechanisms that regulate plant productivity, growth and yield under field conditions and stress
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37 584 combination. A fundamental key will be understanding the metabolic, cellular, and developmental
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39 585 pathways utilized by plants to respond to and interact with their dynamic environment, pathogens,
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41 586 and pollinators. New and modified crop varieties and cultivars must have a “balanced” genetic
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43 587 content that will alleviate the losses caused by single, as well as combined environmental stresses,
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45 588 pests and other rapidly changing environmental conditions. Some of the important objectives
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47 589 include increasing photosynthetic efficiency, altering stomatal regulation, creating a balanced and
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49 590 efficient use of nutrients and water, and encouraging interactions of plants with beneficial
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51 591 microorganisms (Figure 4, Table S2). Some of the possible avenues to increase plant productivity
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53 592 and yield in the face of the predicted harsh environmental conditions caused by climate change
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55 593 include, among others:

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58 594 *i)* Enhancing tolerance to stress combinations with special attention to different climate scenarios
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60 595 that include the simultaneous exposure of crops to heat combined with drought, salinity, flooding,

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3 596 high CO₂ levels, and/or pathogen attack. This task will require better understanding of the specific
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5 597 physiological, metabolic and signaling mechanisms involved in crop responses to these stress
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7 598 combinations, as well as understanding the positive and negative interactions between different
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9 599 stresses. Continuous cooperation and open interdisciplinary crosstalk among different researchers
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11 600 will be mandatory for successfully achieving this ambitious goal.

12 601 *ii)* Increasing WUE and NUE, through root, stomata, vascular tissue, and biochemical and
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14 602 regulatory engineering, as well as through enhancing plant-microbiome interactions at the
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16 603 rhizosphere, endosphere and phyllosphere. In this respect, genome-wide studies of crops and
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18 604 microbiomes, coupled with a deep metabolomic analysis and imaging, would be essential.

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20 605 *iii)* Improving plant reproduction and seed filling processes under conditions of stress combination.
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22 606 This goal could be achieved by improving the heat and desiccation tolerance of flowers and by
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24 607 improving allocation of photoassimilates from leaves to flowers. Special emphasis should be given
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26 608 to scenarios of stress combination that include heat stress, since heat was found to have a severe
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28 609 effect on flowering and reproduction.

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30 610 *iv)* Optimizing photosynthetic efficiency by altering the abundance of photosynthetic proteins and
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32 611 minimize photorespiration, contributing to the enhancement of photosynthetic light efficiency and
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34 612 CO₂ assimilation. Additional targets for this goal include, manipulating stomatal density and
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36 613 stomatal aperture control mechanisms, and optimizing light capture by a wider proportion of the
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38 614 plant canopy.

39 615 *v)* Use synthetic biology, nanoparticle technology, chemistry and advanced artificial intelligence
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41 616 to develop and introduce novel defense and acclimation strategies, currently not present in crop
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43 617 genomes, into our toolbox of means to mitigate climate change.

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45 618 *iv)* Develop, introduce, and improve the use of precision agriculture practices that will enable
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47 619 farmers to mitigate specific aspects of climate change in real time in the field. Included in this goal
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49 620 are improved imaging and mapping technologies, improved robotics and drone technologies, and
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51 621 the development of new chemical application and irrigation methods.

52 622 The development of these future technologies will require more active collaboration between
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54 623 different researchers and institutes worldwide, including ecologists, plant biochemists, molecular
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56 624 biologists and physiologists, breeders, chemists, evolutionary biologists, engineers, computer

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3 625 scientists, bioinformaticians, and many other disciplines. The road ahead is long and challenging,
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5 626 but “climate time” is upon us.
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10 628 **Data statement**

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12 629 All relevant data can be found within the manuscript.
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15 630

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32 638 **Authors' contributions**

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35 639 RMR, EB, RM and SIZ wrote the manuscript and designed the figures.
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40 641 **Conflict of interest statement**

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43 642 The authors declare no conflict of interest.
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47 644 **Supporting Information**

48
49 645 Table S1. Environmental and socio-economic impacts of global warming and climate change.
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51 646 Table S2. Proposed strategies for the development of climate resilient crops.
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1186 **Figure legends**

1187 **Figure 1.** Global warming and climate change are likely to subject crops, trees and other plants to
1188 the sequential or simultaneous effects of stress combination. (a) The manifestation of climate
1189 change is different at different regions around the globe and could include the simultaneous or
1190 sequential occurrences of two or more different stresses including heat waves, flooding, drought
1191 and/or salinity. Data was obtained from www.climate.gov, NOAA and Hassani *et al.*, (2020). (b)
1192 Potential stress combinations could involve different biotic factors (*e.g.*, virus, bacteria, insect...),
1193 climate change-driven weather events (*e.g.*, flooding, extended droughts, heat waves...), man-
1194 made anthropogenic stresses (*e.g.*, pesticides, antibiotic, heavy metal...), and/or soil-associated
1195 stress condition (*e.g.*, nutrient deficiency, salinity, decreased microbial diversity...). In different
1196 combinations, these environmental stress conditions could negatively impact yield and cause food,
1197 feed, and fiber shortages. Adapted from Zandalinas *et al.*, (2021a).

1198 **Figure 2.** The effects of different stress combinations on stomata and reproduction processes, and
1199 the beneficial effects of the plant microbiome. (a) Effects of individual stresses and different stress
1200 combinations on stomatal regulation in plants. Modified from Balfagón *et al.*, (2020). (b) Climate
1201 change-driven stress combinations negatively impact plant reproduction, resulting in reduced
1202 yields. Some of the reproductive processes affected by climate change include pollen maturation,
1203 germination and overall viability, fertilization, embryogenesis, seed filling, and plant-pollinators
1204 interactions. (c) Schematic overview of some of the beneficial effects of the plant microbiome that
1205 could potentially mitigate the impacts of global warming and climate change on plants.
1206 *Abbreviations:* ABA, abscisic acid; CK, cytokinin; IAA, indol-acetic acid; NUE, nitrogen use
1207 efficiency; ROS, reactive oxygen species; WUE, water use efficiency.

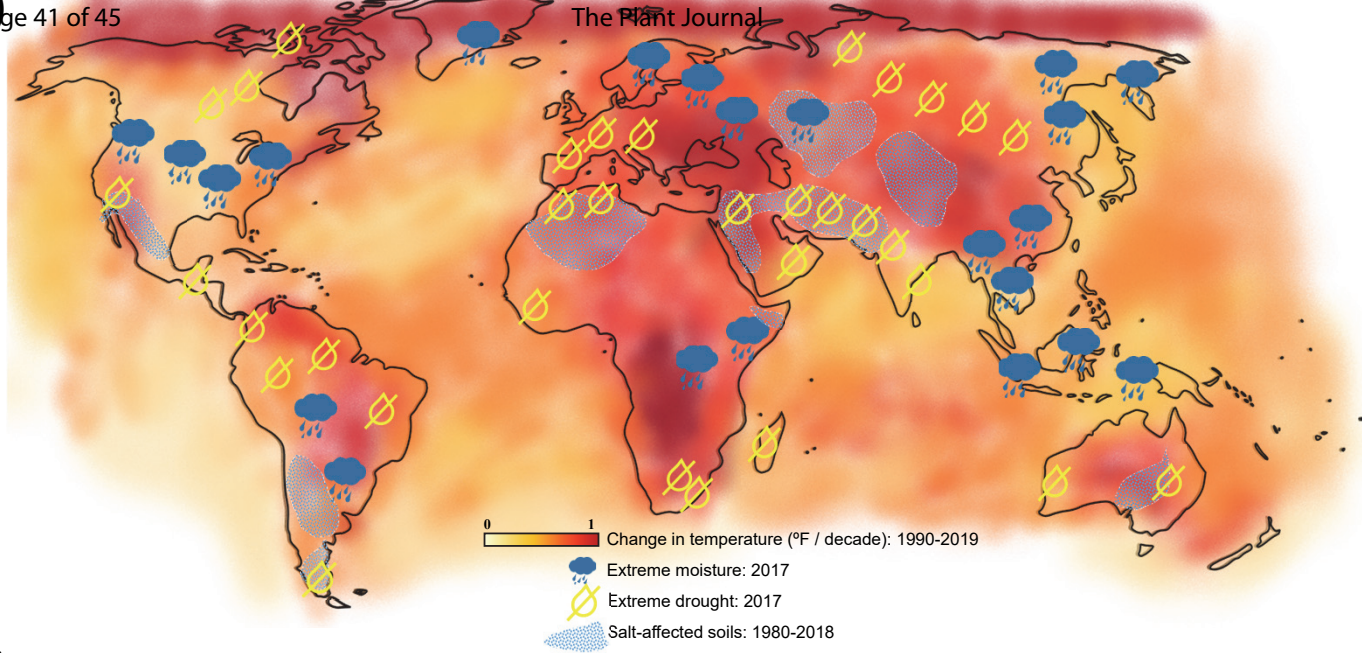
1208 **Figure 3.** Global warming, climate change and environmental pollutions present plants with
1209 multiple combinations of different abiotic and biotic stresses that could have a detrimental effect
1210 on plants, soils, and microbial populations. (a) Multifactorial stress combination is under-
1211 represented in studies of plant stress interactions. The graph shows the number of studies focused
1212 on single or multiple stress factors between 1957 and 2017. Adopted from Rillig *et al.*, (2019b).
1213 (b) An increase in the number of stressors acting simultaneously (multifactorial stress
1214 combination; orange) results in a decrease in plant survival, soil properties and microbial diversity

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3 1215 (blue). Based on the studies of Rillig et al., (2019b) and Zandalinas *et al.*, (2021a,b). (c) Heat map
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5 1216 showing the expression level of different WRKY transcription factors in response to multifactorial
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7 1217 stress combinations of salt, paraquat, heat stress, high light, acidity, and cadmium. (d) Venn
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9 1218 diagrams showing the overlap between genes upregulated in their expression in response to
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11 1219 different 3 factor stress combinations (left), or 4-, 5- and 6- factor stress combinations (right).
12 1220 Stresses include salt, paraquat, heat stress, high light, acidity and cadmium. Transcriptomics data
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14 1221 was adapted from Zandalinas *et al.*, (2021b). *Abbreviations:* A, acidity; Cd, cadmium; HL, high
15 1222 light; HS, heat stress; PQ, paraquat.

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18 1223 **Figure 4.** Proposed strategies for the development of climate resilient crops. Strategies include
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20 1224 bioengineering plants (*e.g.*, overexpressing key genes involved in abiotic stress-tolerance),
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22 1225 applying biostimulants including chemical, hormones or nanoparticles; modifying the plant
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24 1226 microbiome (*e.g.*, using inoculants); and improving flower performance by metabolic engineering
25 1227 or increasing flora visitation by pollinators. See also Table S2.

IDENTENTIAL

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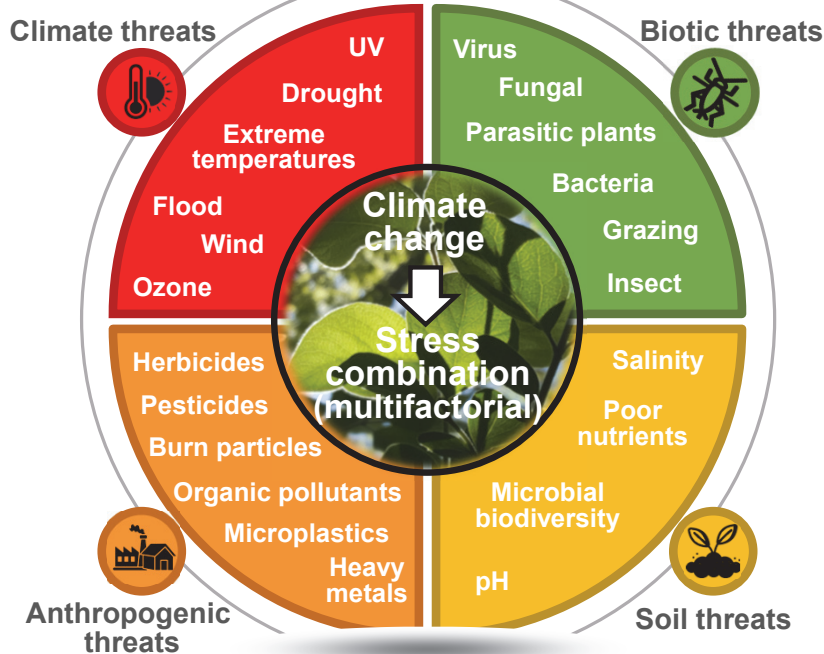
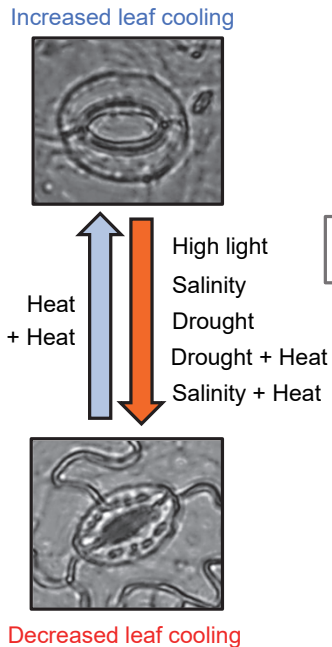
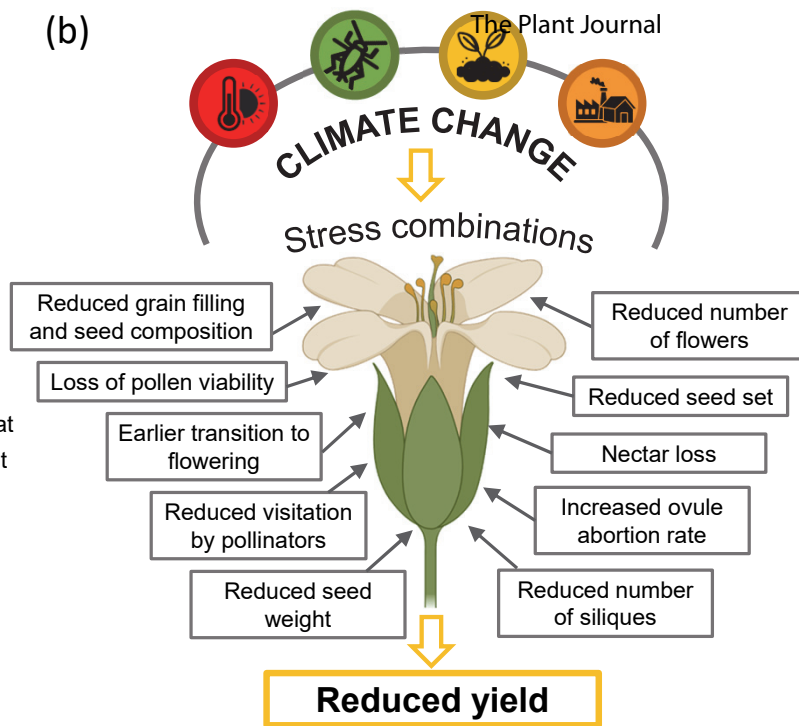


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(a)



(b)



(c)

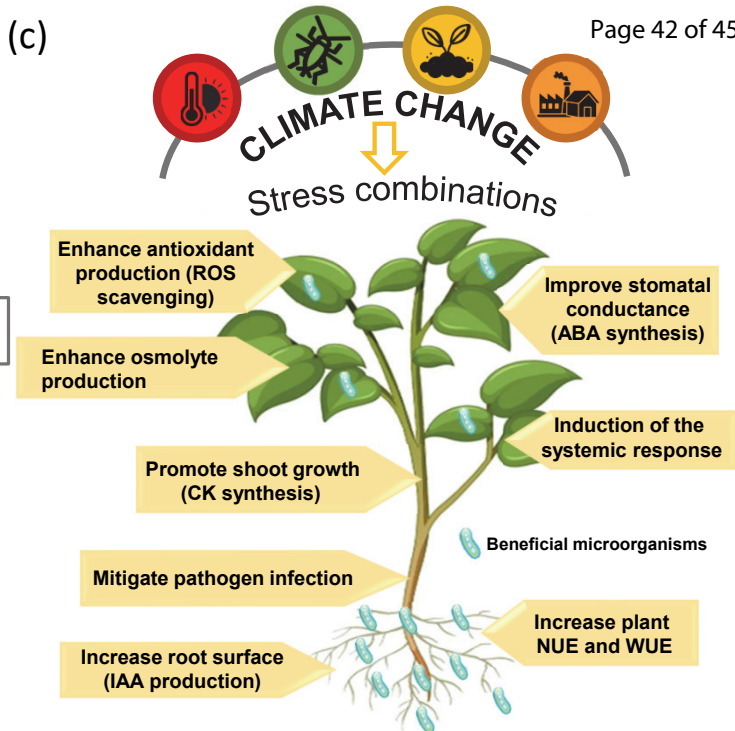


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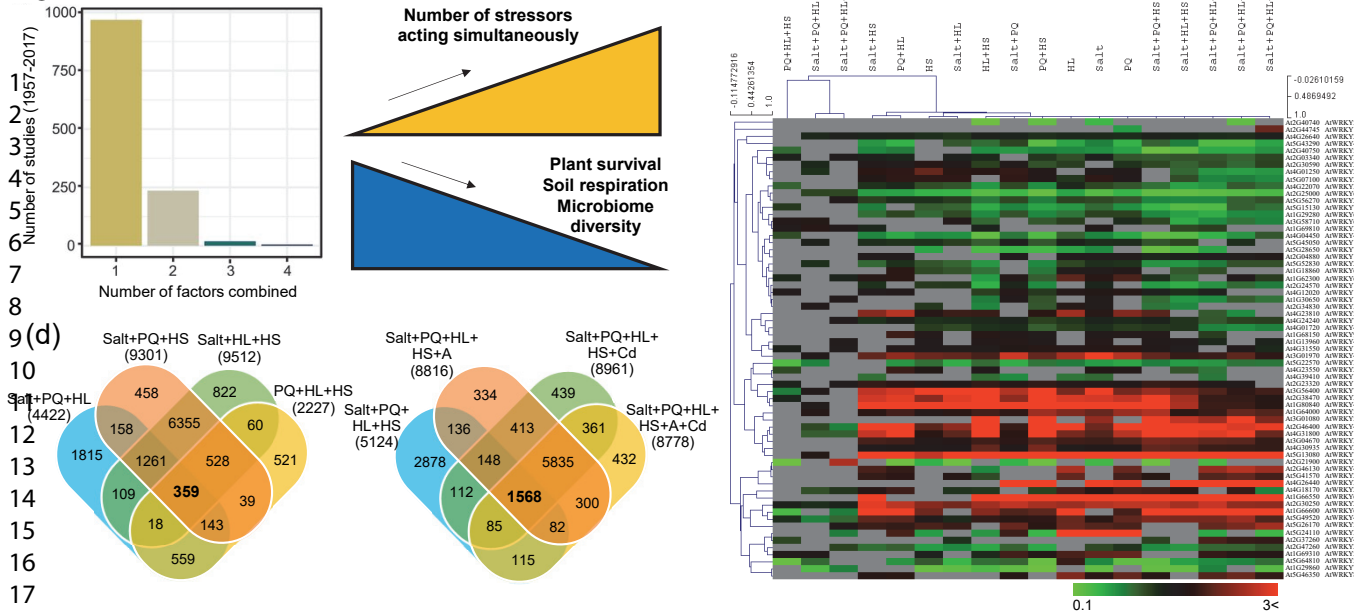


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MITIGATION STRATEGIES

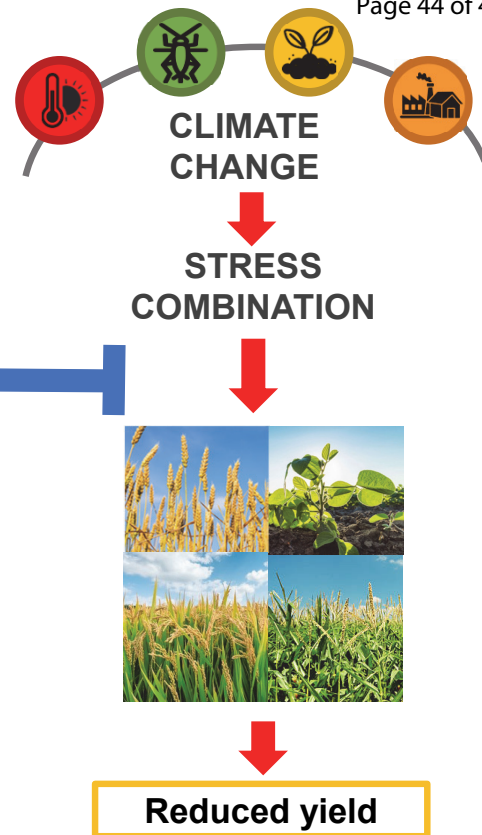
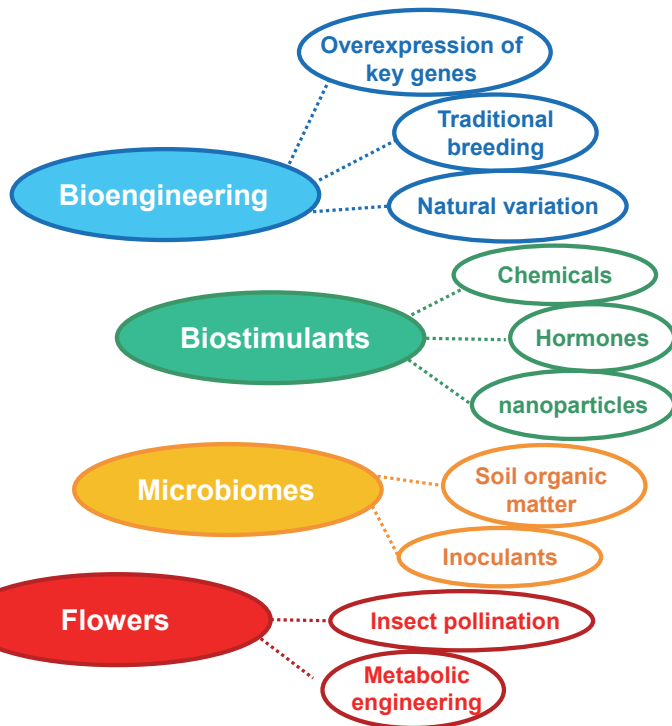
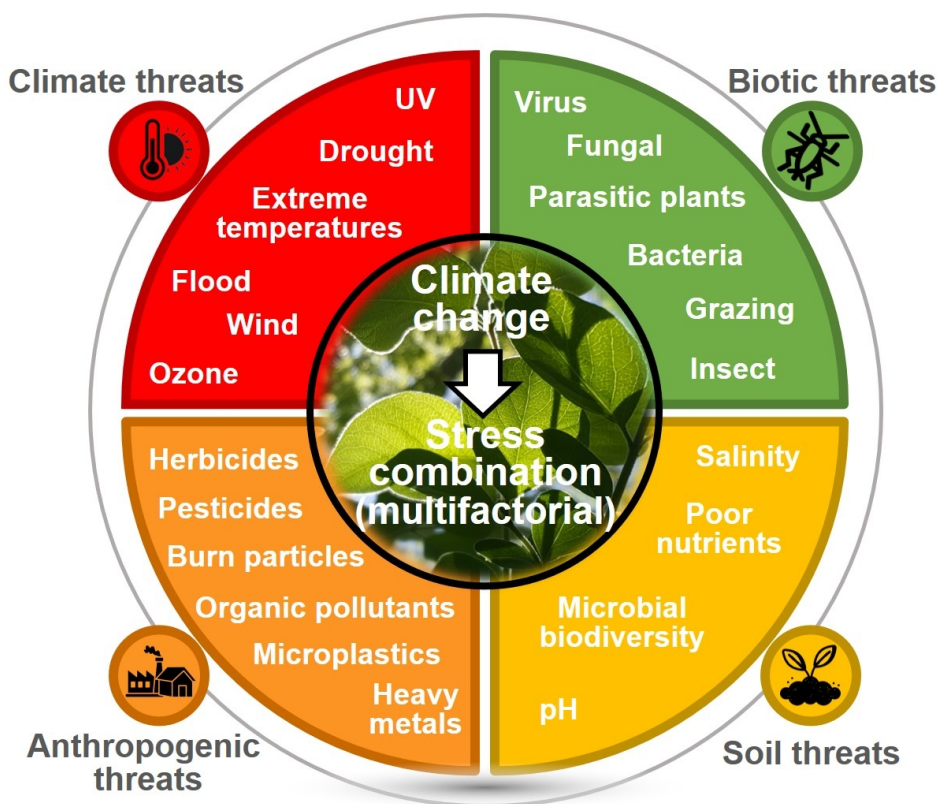


Figure 4. Proposed strategies for the development of climate resilient crops. Strategies include bioengineering plants (e.g., overexpressing key genes involved in abiotic stress-tolerance), applying biostimulants including chemical, hormones or nanoparticles; modifying the plant microbiome (e.g., using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

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