Tansley insight

Plant responses to multifactorial stress combination

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Summary

Human activity is causing a global change in plant environment that includes a significant increase in the number and intensity of different stress factors. These include combinations of multiple abiotic and biotic stressors that simultaneously or sequentially impact plants and microbiomes causing a significant decrease in plant growth, yield, and overall health. It was recently found that with the increasing number and complexity of stressors simultaneously impacting a plant, plant growth and survival dramatically declines, even if the level of each individual stress, involved in such 'multifactorial stress combination', is low enough to not have a significant effect. Here we highlight this new concept of multifactorial stress combination and discuss its importance for our efforts to develop climate change-resilient crops.

Keywords: Abiotic stress, Biotic stress, Climate change, Crop, Global warming, Multifactorial stress combination, Pollution, Stress combination.

I. Introduction

In the past 150 years, humans had a profound effect on Earth biota and ecosystems causing massive habitat loss, pollution, overexploitation, introduction of invasive species, and climate change (IPCC 2021). These changes significantly eroded biodiversity, triggering concerns that we are in the midst of a sixth mass extinction (Sage, 2020; Wagner *et al.*, 2021). Although each of the individual drivers or stressors, indicated above, could potentially have a negative effect on any given ecosystem or plant species, many of these stressors were proposed to interact with each other (*e.g.,* Côté *et al.,* 2016; Rillig *et al.,* 2021b). These interactions could be synergistic, antagonistic, or additive. Synergy in this context occurs when the combined effect of multiple stressors exceeds that of the sum of the effects of each individual stressor (applied individually). In contrast, antagonistic interactions imply that when different stressors are combined, their overall impact is less than the sum of the effects of each individual stressor (applied individually), while additive means that the combined effect of multiple stressors is equal to that of their sum. Although many ecologists and conservationists tend to emphasize the negative cost of synergistic interactions between different stressors on our ecosystems, care should be exercised in interpreting and over emphasizing these interactions (Côté *et al.*, 2016). In this Tansley Insight article we focus on synergy and antagonism between multiple stressors and drivers with a focus on plants. Readers interested in other types of interactions are referred to (Côté *et al.*, 2016; Zhou *et al.*, 2020).

At least two different examples for synergistic interactions between multiple global stressors have recently been discussed and highlighted in the literature. One pertains to the Indian River lagoon ecosystem in Florida that is home to many important fish, mammal, and bird species, including 70% of the U.S. Atlantic coast population of Florida manatees. This ecosystem has been subjected to multiple stressors including habitat alteration, industrial pollution, toxic spills, and climate change. Synergistic interactions between these drivers caused harmful algal blooms, which in turn caused major seagrass die-offs and large-scale marine, mammal, bird, and fish kills (Adams *et al.*, 2019). A second example for synergistic interactions between global change stressors is the major die-off of forests in Europe. These have been subjected in recent years to a lethal combination of major storms followed by an extended drought, attack by insects, and fires (Huang *et al.*, 2020; Hamann *et al.*, 2021; Popkin, 2021). Additional smaller-scale studies have also revealed that a combination of multiple stressors can have a synergistic effect on microbiomes, soils, plants, and animals (*e.g.*, Rillig *et al.*, 2019; Defo *et al.*, 2019; Vanbergen *et al.*, 2021; Zandalinas *et al.*, 2021b). Here we will discuss the synergetic and antagonistic effects of multiple stress factors on plants. For an excellent Viewpoint article on the synergistic effects of multiple stress factors on plant-microbiome interactions, the reader is referred to Rillig *et al.*, (2021a).

II. Synergistic and antagonistic effects of stressors on plants: From simple stress combinations to multifactorial stress.

The basic concept of stress combination in plants was addressed at the physiological level in early studies that considered different biotic, abiotic, and anthropogenic effects (*e.g.*, Mooney *et al.*, 1991; Nilsen & Orcutt, 1996). By contrast, molecular studies of stress combination in plants begun about 20 years ago with a focus on drought and heat stress combination (Rizhsky *et al.*, 2002, 2004). This stress combination has a long history of causing massive yield losses to agricultural production, is a major goal for plant breeders, and results in conflicting pressures on plant physiology and metabolism (*e.g.*, Mittler, 2006; Mittler & Blumwald, 2010; Zandalinas *et al.*, 2016). It can also serve as an excellent example for the opposing pathways triggered in plants during stress combination. A key example for these is stomatal regulation. While heat stress causes stomata to open, so that plants can cool themselves by transpiration, drought stress induces an opposing response (*i.e.,* stomatal closure), to prevent water loss. During drought and heat stress combination, stomata on leaves remain closed (drought pathways overcome heat pathways) and leaf temperature rises to dangerous and sometimes lethal levels (Rizhsky *et al.*, 2002, 2004; Mittler, 2006; Zandalinas *et al.*, 2020b). In contrast, a recent study found that although stomata on leaves close during a combination of drought and heat stress, stomata on flowers remain open and flowers can maintain transpiration, cooling reproductive tissues (representing a new acclimation strategy in plants termed 'differential transpiration'; Sinha *et al.*, 2022). The initial studies of drought and heat stress combination were followed by studies of many other stress combinations of two or at most three different stresses applied simultaneously to plants (akin to the effects of multiple stressors on the Indian River lagoon ecosystem in Florida; *e.g.,* Prasch & Sonnewald, 2013; Suzuki *et al.*, 2016; Shaar-Moshe *et al.*, 2017; Zhang & Sonnewald, 2017; Balfagón *et al.*, 2019; Zandalinas *et al.*, 2020a,b). Additional studies have also examined the effect of different stresses occurring in sequence on plants (somewhat similar to the effects of storms followed by extended drought, followed by insect attack and fires on forests in Europe; *e.g.,* Coolen *et al.*, 2016).

While a few of the studies described above revealed that in some cases of stress combination the effect of one stress (*e.g.,* drought) was dominant to the others, many studies (*e.g.,* a combination of drought and heat) revealed a synergistic effect of the stress combination on plant growth, survival and yield (Mittler, 2006; Mittler & Blumwald, 2010; Zhang & Sonnewald, 2017). It was also found that in some cases of stress combination two different stressors may have an antagonistic effect on each other, for example during drought combined with ozone or pathogen infection (drought causing stomatal closure that prevents ozone or pathogens from entering the plant; Gupta *et al.*, 2016). Interestingly, while some stress combinations had a synergistic effect on one plant species (*e.g.*, a combination of heat and salinity on Arabidopsis; Suzuki *et al.*, 2016), the same stress combination had an antagonistic effect on a different plant species (*i.e.*, tomato; Rivero *et al.*, 2014). The intensity of each stress involved in the combination, the order in which the stresses are applied to the plant, and the plant species involved, could therefore determine whether a stress combination would have synergistic, antagonistic, or additive effect (Mittler, 2006; Mittler & Blumwald, 2010; Zhang & Sonnewald, 2017; Zandalinas *et al.*, 2020b). In recent years a new and important avenue in the study of plant stress combination opened, *i.e.*, multifactorial stress combination (Zandalinas *et al.*, 2021a,b). The approach of multifactorial stress combination emerged from the realization that due to human interference, the complexity of stressors in the plant environment increases dramatically and a simple approach of two- or at most three-stress combinations may no longer suffice (Fig. 1; Zandalinas *et al.*, 2021a).

III. Survival and stress responses during multifactorial stress combinations: New findings and a dire warning

Some of the multiple stressors that could potentially impact plants during a multifactorial stress combination are depicted in Fig. 1. Considering the sharp increase in the number of global change stressors in the past 150 years, it is not hard to envision how different combinations of 3, 4, 5 or more of some of these could impact plants simultaneously or sequentially. The frequency and intensity of many of the stress combinations depicted in Fig. 1 (*e.g.,* heat waves or cold snaps combined with drought or flooding) has already been shown to increase due to climate change, and many of these stress combinations already occur on the background of soils with poor nutritional content, high levels of salinity, and/or extreme pH (Mazdiyasni & AghaKouchak, 2015; Bailey-Serres *et al.*, 2019; Alizadeh *et al.*, 2020; Zandalinas *et al.*, 2021a; IPCC 2021). In addition, the level of many different air, water, and soil pollutants, with negative impact on plants, is increasing in our environment (*e.g.,* microplastics, persistent organic compounds, heavy metals, antibiotics, and ozone), and the weakening of plants, or the shifting of weather patterns, a consequence of global warming and climate change, subject plants to additional biological threats such as insect attacks and pathogen outbreaks (Rillig *et al.*, 2019, 2021b; Huang *et al.*, 2020; Hamann *et al.*, 2021; Zandalinas *et al.*, 2021a). In addition to impacting the plant directly, many of these stressors could impact the plant microbiome that plays an important role in promoting plant germination, growth, reproduction, and overall survival (Rillig *et al.*, 2019, 2021a; Yang *et al.*, 2021). The complexity, composition, and overall abundance of soil microbiomes was for example shown to decline with the increasing number of global stress factors impacting an ecosystem (Rillig *et al.*, 2019).

Because different stress factors can have different effects on plant physiology and metabolism, it is not hard to envision how a combination of many different stresses will have an additive effect on plants leading to a dramatic decrease in growth and productivity (Fig. 2a). However, as depicted in Fig. 2b, and reported in multiple publications, different stresses can have synergistic or antagonistic effects on each other (Mittler, 2006; Mittler & Blumwald, 2010; Zhang & Sonnewald, 2017). While some of the known synergistic or antagonistic interactions between two different stresses (depicted in a simple stress matrix in Fig. 2b) may be preserved or amplified when two or more stresses are added to the mix to create a multifactorial stress combination, some interactions may be completely altered. For example, the sometimes-antagonistic effects between drought and pathogen could be preserved or amplified in the presence of ozone or other stressors that enter plants through stomata, while the sometimes-synergistic effects between high light and heat could be preserved or amplified by salinity or heavy metals that will have a higher uptake rate into the plant because of enhanced transpiration. In contrast, some antagonistic effects, for example between high light and pathogen (high light causing stomatal closure and preventing pathogen entry), could become synergistic in the presence of heat stress that will cause stomatal opening (heat stress-driven stomatal regulation, *i.e.*, opening, overcomes high light-driven stomatal regulation, *i.e.*, closure, and stomata are kept open; Balfagón *et al.*, 2019). Some studied and/or hypothetical antagonistic or synergistic interactions between different stresses and their combinations during multifactorial stress combination are depicted in Fig. 2b.

To study the impact of multifactorial stress combination on plant growth and survival, Zandalinas *et al.*, (2021b) recently studied the impact of a combination of six different abiotic stresses (heat, high light, salinity, acidity, cadmium, and oxidative stress induced by the herbicide paraquat) simultaneously applied in different combinations to *Arabidopsis thaliana* seedlings grown on agar plates or in peat soil. Their study revealed that reactive oxygen species (ROS) metabolism plays a key role in plant resilience to stress combination, and that the transcriptomic response of plants to different combinations of stresses is unique and cannot be predicted from the transcriptomic response of plants to each of the different stresses (involved in the multifactorial stress) applied individually. In addition, it was found that during high order stress combinations, involving three or more stresses, many unique genes are upregulated, while some ‘classical’ pathways for stress response and acclimation are suppressed. Perhaps the most dramatic and worrisome finding originating from this study was however the synergistic interactions between multiple low-level stresses (Zandalinas *et al.*, 2021a,b). Thus, while each of the different stresses applied individually to plants had a negligible effect on plant growth and survival, with the increase in the number and complexity of stresses combined, plant growth and survival declined. This decline was initially slow, but dramatically increased when four or more stresses were combined (Fig. 3a). The reason this finding is worrisome is that we may not be able to predict how different stressors could impact a plant or an ecosystem until it might be too late. For example, while one or even two low level stressors may have no significant effect on an agricultural area or an ecosystem, adding a low level of one or two additional stressors (each without an apparent effect when applied individually) could cause an unexpected and dramatic decline in yield or ecosystem health.

IV. Concluding remarks and future perspectives

The experimental work of Zandalinas *et al.*, (2021b) appeared to have revealed a new principle in plant biology. This principle states that with the increase in the number and complexity of stressors impacting a plant, plant growth and survival will dramatically decline, even if the level of each individual stress involved in the multifactorial stress combination is low enough to not have a significant effect on plant growth and survival (Fig. 3a). A similar synergistic principle of multifactorial stress combination was previously demonstrated experimentally for soil microbiomes by Rillig *et al.*, (2019; Fig. 3b), and could therefore also impact plant-microbiome interactions (Rillig *et al.*, 2021a). Of course, when it comes to entire ecosystems that have a high level of biodiversity, the outcomes of multifactorial stress combination could vary, depending on the species and stresses involved. However, when it comes to large agroecosystems such as crop fields, that have a very low biodiversity, *i.e.*, one dominant plant species (the crop), the outcome of multifactorial stress combination is likely to be negative (*i.e.*, synergistic). The findings that multifactorial stress combinations can have an adverse effect on plants, microbiomes, and their potential interactions should serve as a dire warning to our society. If we will not be careful to limit the number and intensity of the different stressors we introduce into our environment, we may find ourselves living on a planet that cannot support the rapid increase in the growth of our own species (Lobell *et al.*, 2011; Challinor *et al.*, 2014; Bailey-Serres *et al.*, 2019; Zandalinas *et al.*, 2021a).

The initial observations made by Rillig *et al.*, (2019) and Zandalinas *et al.*, (2021b) should be followed and substantiated by additional studies addressing the impact of additional and different multifactorial stress combinations on different plant species, microbiomes, and crops. A heightened awareness of these alarming observations is also needed by the scientific community, funding agencies, and policy makers. It is likely that a multipronged approach that includes breeding and/or engineering plants for resilience to multifactorial stress combination, increasing the diversity of different crops used in agriculture (increased biodiversity), and manipulating plant-microbiome interactions, will help in mitigating some of the effects of multifactorial stress combination on plant yield and overall health (Fig. 4; Zsögön *et al.*, 2021; Rivero *et al.*, 2022). Such an approach would integrate laboratory, growth chamber, greenhouse, and field experiments of plant responses to multifactorial stress combination with genome-wide association studies (GWAS) of different crops and plants subjected to stress combination, as well as with the collection of new biological material in the form of wild plant varieties and microbiomes from different sites or areas subjected to multifactorial stress combination (Fig. 4). The genes, pathways and networks identified by these studies, together with the rich genetic variability offered by the wild varieties and microbiomes, could then be leveraged in new breeding efforts to increase the resilience of crops to multifactorial stress combination (Fig. 4). Novel methods and concepts that utilize knowledge from other research fields such as material sciences, nanotechnology, physics, and chemistry, as well as the use of advance precision agriculture methods, and an overall effort to mitigate some of the stressors that cause multifactorial stress combination, could complement the breeding efforts and shield different plants and crops from the devastating effects of multifactorial stress combination (Fig. 4). With additional knowledge and time (that we may not have due to the increased rate in anthropogenic activity; IPCC 2021) we should be able to overcome the challenge of multifactorial stress combination. However, the road is long, and the time is short, so we better be in a hurry.

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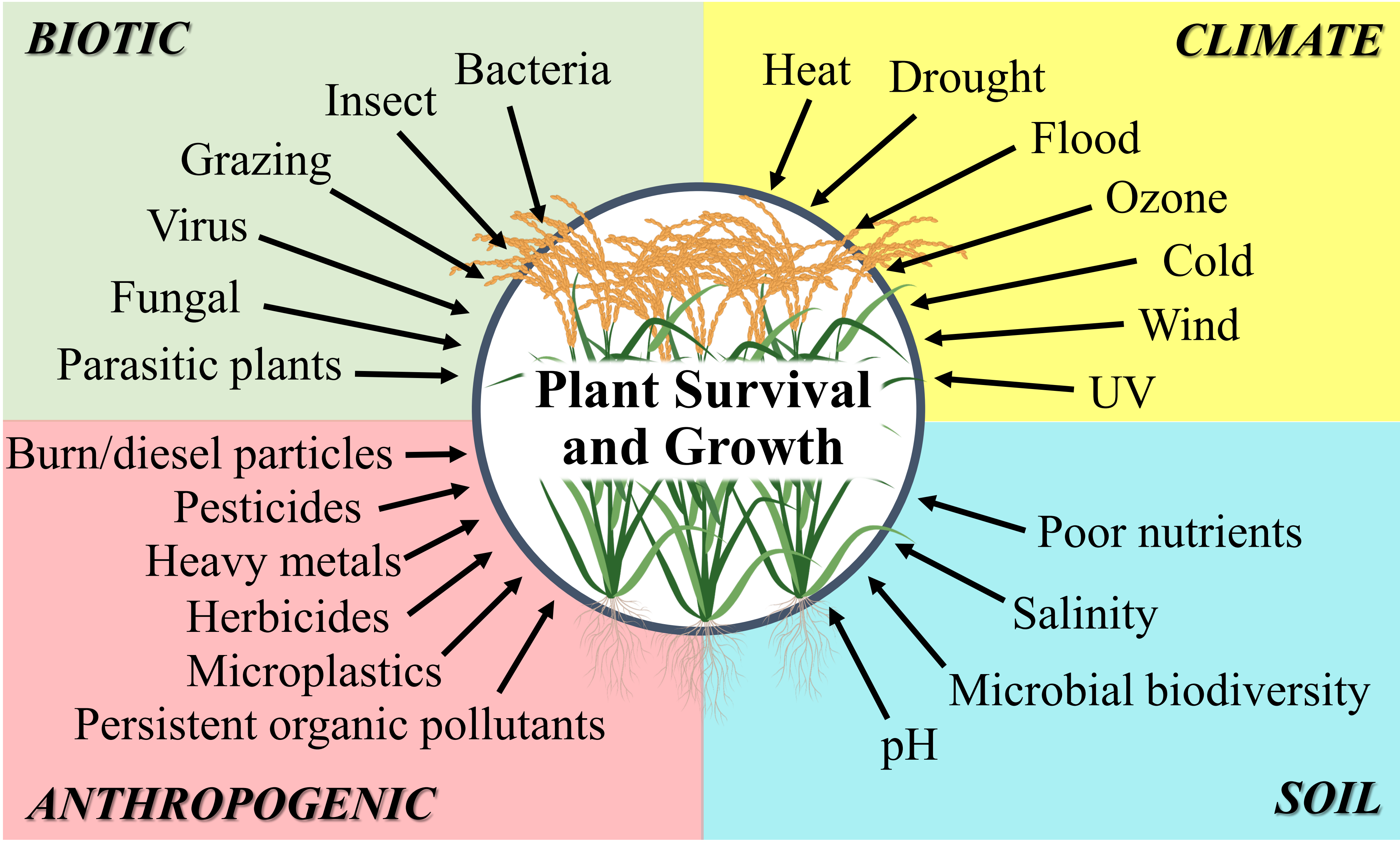
Figure Legends

Fig. 1 Biotic-, climate- soil- and anthropogenic-driven stressors that may impact plants simultaneously or sequentially, in different combinations, and cause a state of multifactorial stress combination. The intensity, duration, and complexity of many of the stresses outlined is likely to increase in the coming years due to human activity. In different combinations, many of these stresses could cause a rapid decline in plant health, growth, productivity, and overall survival, especially when it comes to large agroecosystems that support a single plant (crop) species.

Fig. 2 Additive, synergistic and antagonistic effects of multifactorial stress combination on plants. (a) A hypothetical model showing the additive effects of different stress factors on basic biological processes of plants. Note that different stresses can have different and sometimes opposing effects on transpiration that could result in negative synergistic effects during multifactorial stress combination. (b) The effect of adding one or two more stressors (air and/or soil pollution) to experimentally tested, or hypothetical, antagonistic and synergistic interactions between two different stresses (presented as a simple stress matrix; top left). The combinations of four different stresses (matrix on bottom right) are hypothesized to be all negative.

Fig. 3 The synergistic effects of increasing the number of stressors simultaneously affecting plants and ecosystems. (a) The plant multifactorial stress principle: With the increase in the number and complexity of stressors impacting a plant (X-axis), plant survival will dramatically decline (Y-axis), even if the level of each individual stress involved in the multifactorial stress combination is low enough to not have a significant effect on plant growth and survival. Based on Zandalinas *et al.*, (2021a,b). (b) The synergistic effects of multiple stressors on ecosystem processes: With the increase in the number and complexity of stressors impacting an ecosystem (X-axis), ecosystem processes will dramatically decline (Y-axis). Adapted from Rillig *et al.*, (2019).

Fig. 4 Multipronged approach to induce resilience of plants and crops to multifactorial stress combination. An integration of different approaches to study multifactorial stress combination, including direct experimentation, genome-wide association studies (GWAS), and collection of biological material in the form of wild varieties and microbiomes will help in identifying genes, pathways and networks associated with the response of plants to stress combination and support the breeding of crops to withstand multifactorial stress combination. These efforts will be complemented by novel approaches and concepts from other fields, such as chemistry, physics, material sciences and nanotechnology, the use of precision agriculture practices, and an overall effort to reduce the complexity and number of stress factors impacting plants. These will help in identifying novel ways of shielding plants from the effects of multifactorial stress combination.



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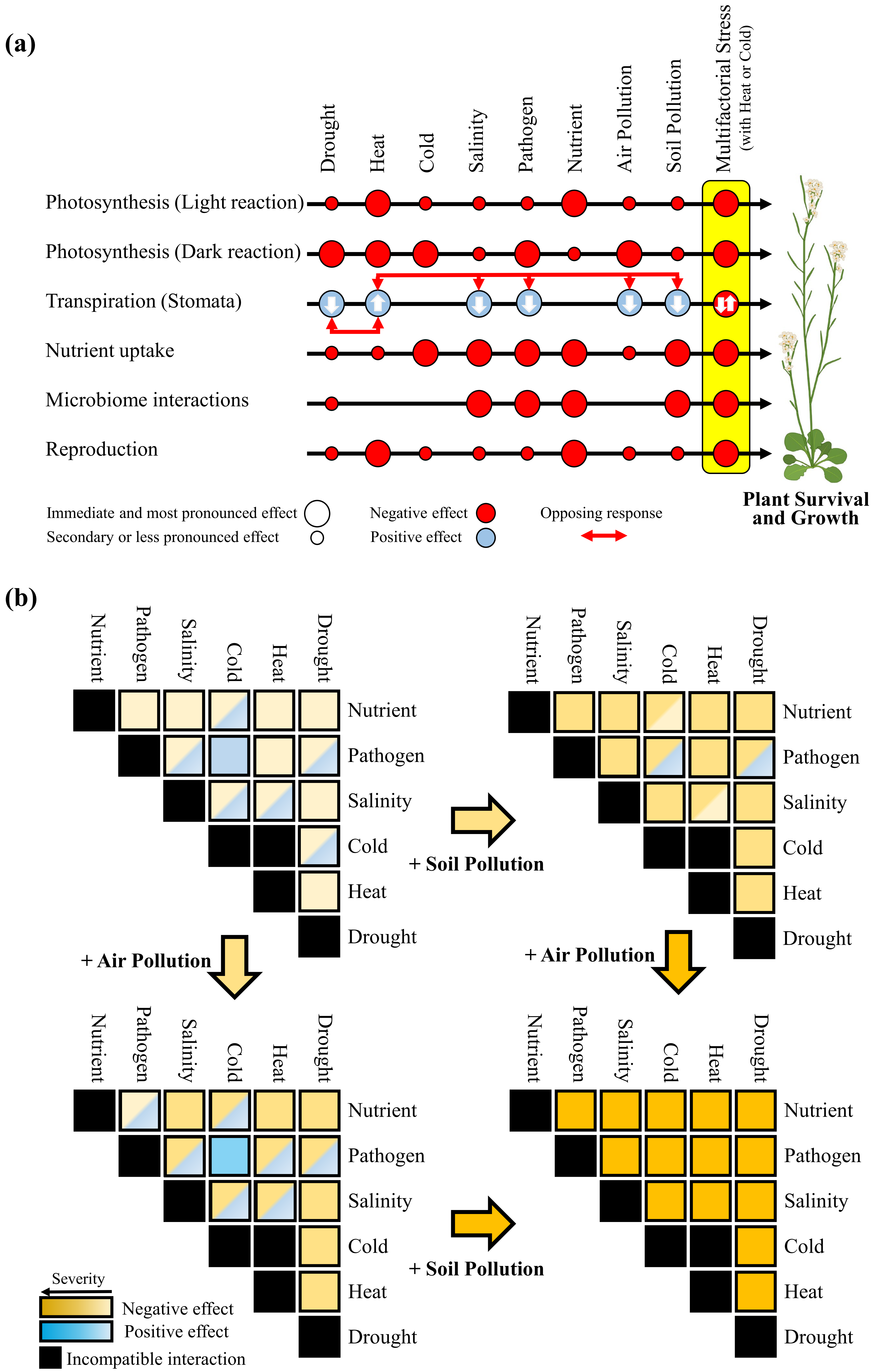

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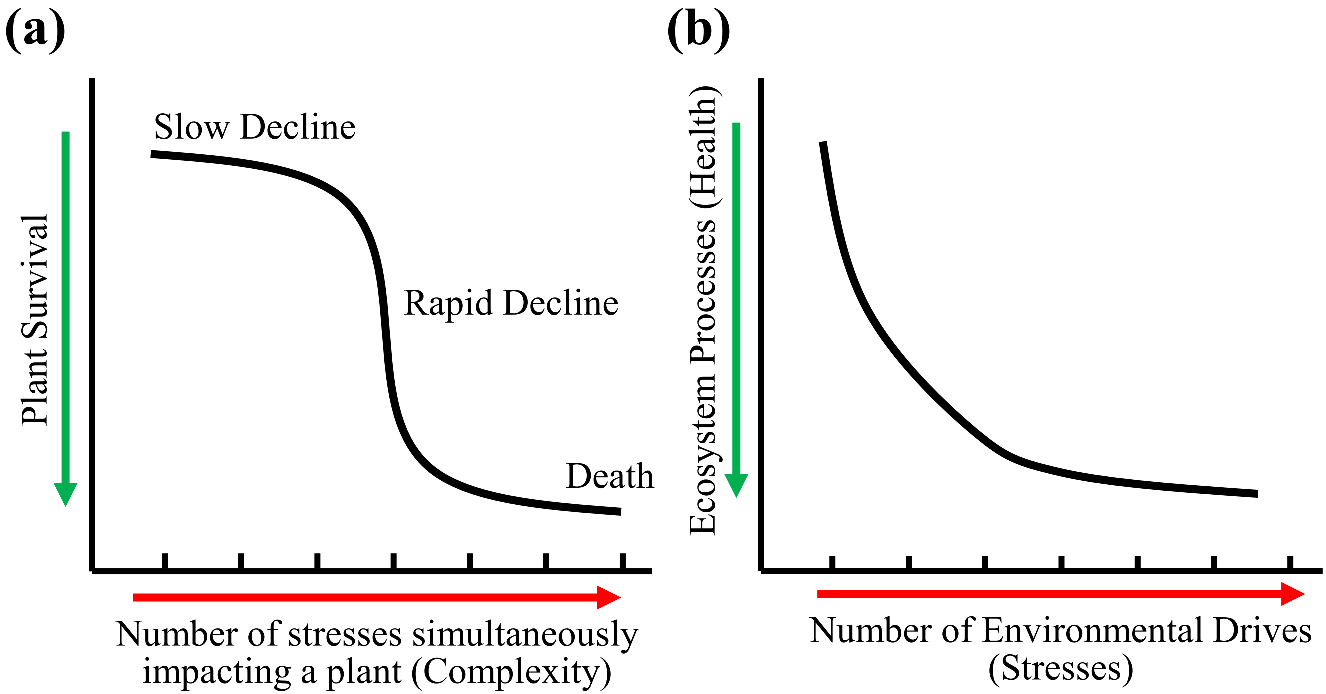

Fig. 3 The synergistic effects of increasing the number of stressors simultaneously affecting plants and ecosystems. (a) The plant multifactorial stress principle: With the increase in the number and complexity of stressors impacting a plant (X-axis), plant survival will dramatically decline (Y-axis), even if the level of each individual stress involved in the multifactorial stress combination is low enough to not have a significant effect on plant growth and survival. Based on Zandalinas *et al.,* (2021a,b). (b) The synergistic effects of multiple stressors on ecosystem processes: With the increase in the number and complexity of stressors impacting an ecosystem (X-axis), ecosystem processes will dramatically decline (Y-axis). Adapted from Rillig *et al.,* (2019).

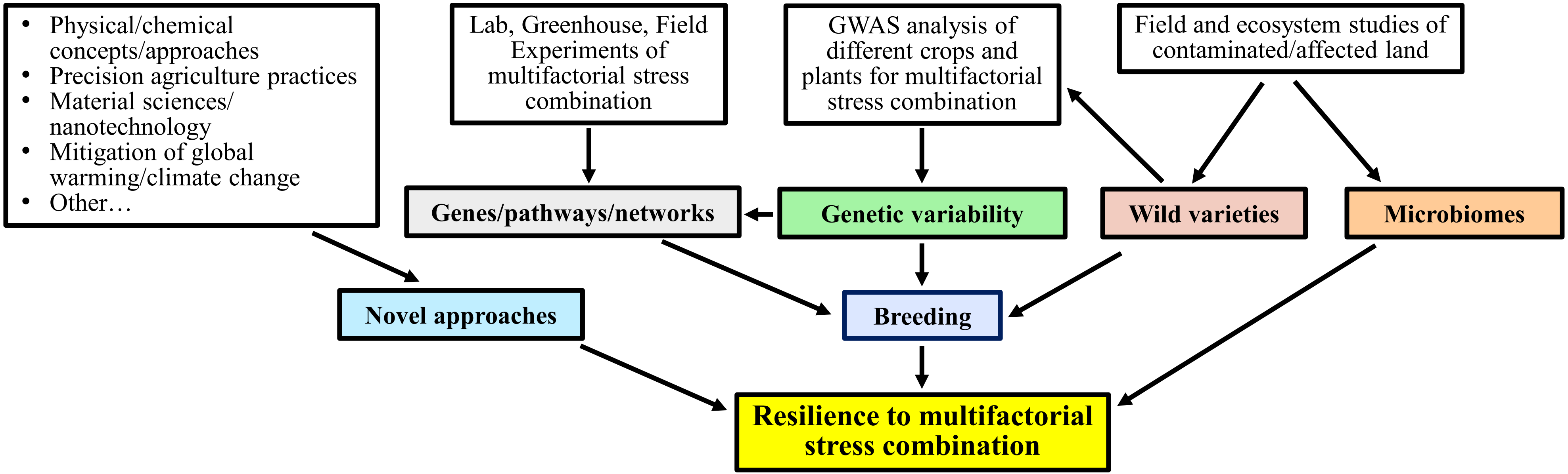

Fig. 4 Multipronged approach to induce resilience of plants and crops to multifactorial stress combination. An integration of different approaches to study multifactorial stress combination, including direct experimentation, genome-wide association studies (GWAS), and collection of biological material in the form of wild varieties and microbiomes will help in identifying genes, pathways and networks associated with the response of plants to stress combination and support the breeding of crops to withstand multifactorial stress combination. These efforts will be complemented by novel approaches and concepts from other fields, such as chemistry, physics, material sciences and nanotechnology, the use of precision agriculture practices, and an overall effort to reduce the complexity and number of stress factors impacting plants. These will help in identifying novel ways of shielding plants from the effects of multifactorial stress combination.