



Activating stress memory: eustressors as potential tools for plant breeding

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Received: 8 December 2021 / Accepted: 26 February 2022 / Published online: 19 March 2022
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Abstract

Plants are continuously exposed to stress conditions, such that they have developed sophisticated and elegant survival strategies, which are reflected in their phenotypic plasticity, priming capacity, and memory acquisition. Epigenetic mechanisms play a critical role in modulating gene expression and stress responses, allowing malleability, reversibility, stability, and heritability of favourable phenotypes to enhance plant performance. Considering the urgency to improve our agricultural system because of going impacting climate change, potential and sustainable strategies rely on the controlled use of eustressors, enhancing desired characteristics and yield and shaping stress tolerance in crops. However, for plant breeding purposes is necessary to focus on the use of eustressors capable of establishing stable epigenetic marks to generate a transgenerational memory to stimulate a priming state in plants to face the changing environment.

Keywords Epigenetic · Stress memory · Eustressors · Plant breeding

Introduction

Agriculture is an important worldwide economic activity that provides us with food, medicines, and a wide variety of materials from fibers to fuels. However, in the last decades, food production faces significant challenges. Despite the increased agricultural productivity, crop production has become insufficient and threatens food security due to the increasing world population. Plus, it is estimated that

worldwide food production will increase by 50–70%, considering that the population is expected to rise to 10.5 billion people by 2050 (Goss et al. 2017; Vos and Bellù 2019). An alternative is to decrease crop losses, which main concerns are abiotic and biotic stresses which tend to intensify in the context of climate change. Biotic stresses, including pathogens and pests, are responsible for losses up to 20% (Goss et al. 2017). For their part, abiotic stresses, which include environmental factors, could limit crop production up to 70% and cause the most critical crop losses worldwide annually by being a major constraint to plant growth and development (Mohanta et al. 2017). Furthermore, climate change will intensify extreme climate events and natural disasters that directly impact the agriculture sector. Over 2008–2018, crop and livestock production loss reached USD 280 billion worldwide, where the main disasters involve drought, floods, storms, landslides, and extreme temperatures, which group 77% of the losses. In contrast, crops pets represent 9% of the losses. Additionally, the recent pandemic COVID-19 disrupted food supply and demand, affecting vulnerable groups, adding urgency to find solutions (FAO 2021).

Therefore, it is essential to transform our current agricultural systems by implementing eco-friendly alternatives to improve crop stress tolerance. Accordingly, potentiating the natural defensive strategies of plants has been considered a

Communicated by Wusheng Liu.

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modern crop approach (Tirnaz and Batley 2019). Plants deal with environmental perturbations constantly, and through time they have adapted, maximizing the phenotypic variation of suitable ecological traits that in adverse conditions are crucial to the population surviving (Parejo-Farnés et al. 2019). Considering that the epigenetic mechanism has a fundamental role in the interactions between genes and the environment in the organism, they can provide novel directions to drive plant-breeding strategies. Epigenetics can help satisfy the demand for crop variations, potentially inducing a broad-spectrum resistance/tolerance, without genetic erosion, and with a gene-mediated balance among resistance and yield (Tirnaz and Batley 2019). Even when the omics technologies and methodologies allowed us to insight into the molecular mechanisms and made punctual modifications in the plant genome, the lack of knowledge of the mechanisms and the biological complexity of the process created uncertainty. However, epigenetic induction can be reached through plant protection products. For this, it is necessary to implement strategies to trigger multigenic defense machinery in an opportune manner, if necessary, and plant biostimulants to promote the development of a diverse range of traits and genotypes more resilient to adverse conditions (Iriti and Vitalini 2021). Among the alternatives to be used are exposures to low doses of stress factors that trigger positive responses in plants, which can be called eustressors. There are different types of eustressor based on their origin: biological, which is classified in elicitors and biostimulants, and non-biological, which can be physical factors or chemical compounds (Vázquez-Hernández et al. 2019). Considering that the beneficial response can be in terms of yield, growth, quality, and stress resistance, and even with multiple benefits on plants, eustressors are a potential tool

to implement in plant breeding programs. However, some aspects are only starting to be discussed: stress memory acquisition in plants by these treatments. In this regard, we will discuss the memory induction potential of eustressors as a new breeding approach based on experimental studies that highlight the stable establishment of epigenetic marks that are useful for agriculture and of physiological responses over multiple generations on plants that are treated with eustressors to promote stress tolerance acquisition. Towards the end, we highlighted some advantages of using these approaches in agricultural systems in the near future.

Concepts: epigenetic, phenotypic plasticity, stress memory, and priming

The term *epigenetics* was proposed by Conrad Hal Waddington in 1942, referring to the study of the interactions between genes and environment in the organism, ergo, the development of characteristics by modification of the patterns of the genome in response to environmental change (Burggren 2016; Parejo-Farnés et al. 2019; Kotkar and Giri 2020). Nowadays, it is known that epigenetic phenomenon is related to biochemical modifications on the genome that determine the conformational state of the chromatin. These epigenetic marks alter the accessibility of the transcriptional machinery and other regulatory elements to the DNA strand, and by consequence, directly or indirectly affect the activation/repression of the genes. The three types of epigenetic marks that are stable and/or inherited: DNA methylation, histone post-transcriptional modifications (PTMs), and the presence of small RNAs (sRNAs), which are schematized in Fig. 1 (Mirouze and Paszkowski 2011; Holeski et al. 2012;

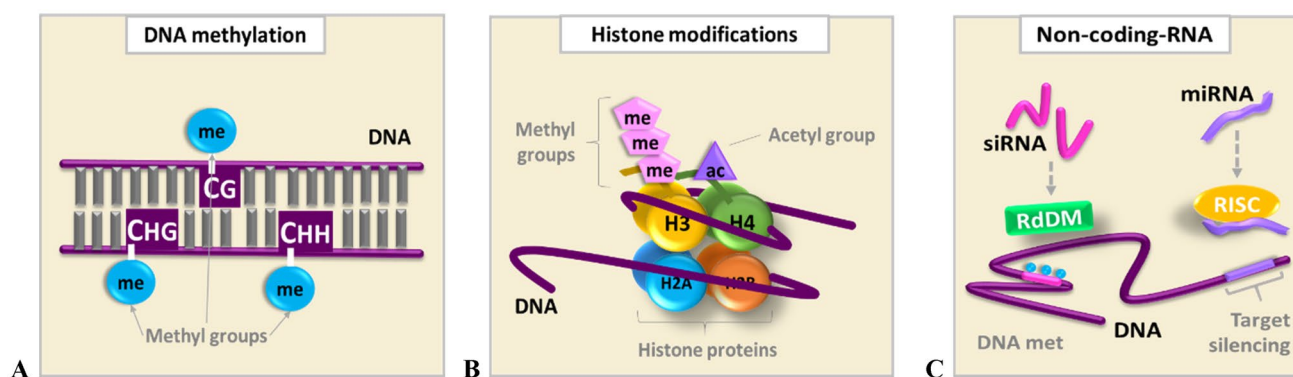


Fig. 1 Epigenetic marks. **A** DNA methylation. It consists of a methyl group on the fifth carbon of cytosines (5-methylcytosine: 5-mC) in the DNA sequence. In plants occurs in three sequence contexts: CG, CHG, and CHH, where the H can be A, T, or C. **B** Histone modifications. It consists of post-translational covalent modifications in the N-tail of histones, like methylation and acetylation, the most studied modifications. **C** Non-coding-RNAs. They correspond to RNA

molecules that do not encode functional proteins but act as gene expression regulators. These are divided based on their biogenesis in micro-RNAs (miRNAs), which are associated with the RNA-induced silencing complex (RISC) to target genes by sequence complementarity, and small-interfering-RNAs (siRNAs), which are involved in de novo methylation of complementary DNA sequences through the RNA-directed DNA-methylation (RdDM) pathway

Pastor et al. 2013; Asensi-Fabado et al. 2017; Gallusci et al. 2017; Lämke and Bäurle 2017; Kumar 2018).

DNA methylation, generally it is considered to cause chromatin condensation, such that the abundance of methyl groups (hypermethylation) is associated with gene silencing and the decrease of it (hypomethylation) with active gene expression (Asensi-Fabado et al. 2017). However, this correlation is not always observed, and there are some cases where an opposite trend was pointed out, like genes up-regulation with hypomethylated regions (Zhang et al. 2006; Zhou et al. 2019; Jiang et al. 2020; Villagómez-Aranda et al. 2021). It is possible that the effect of DNA methylation on gene expression may be determined by the genomic location, the underlying DNA sequence and site class (promoter, body-gene, repetitive sequence, transposon, etc.) and the interplay with other regulatory signals (Bewick and Schmitz 2017). Additionally, other DNA modifications have been identified: 5-hydroxymethylcytosine (5-hmC) (Kumar 2018) and N6-methyladenine (6-mA), which does not have a definitive role, but it has been associated with active gene expression of stress-related genes (Zhang et al. 2018; Zhou et al. 2018). By contrast, histone PTMs are very varied: there exist eight types of modifications (acetylation, methylation, phosphorylation, ubiquitination, sumoylation, ADP-ribosylation, deamination, and proline isomerization) and over 60 different residues on histones where modifications occur (Kouzarides 2007). The most studied histone PTMs are histone acetylation, which is associated with active gene transcription, and histone methylation, which effect varies depending on the methylation site. For instance, histone methylation on H3K9 (9th lysine on H3) and H3K27 is associated with transcription repression; however H3K4 and H3K36 are marks associated with transcription activation (Fujimoto et al. 2012). Eventually, the non-coding RNAs regulate gene expression at the post-transcriptional level. There are a wide variety of these molecules. At the first stage, they divide into housekeeping and regulatory non-coding RNAs. The last is divided based on the size in short-chain non-coding-RNAs, which include siRNAs, miRNAs and piRNAs, and long chain non-coding RNAs. The most studied ones are siRNAs and miRNAs, but all of them have a gene expression regulatory role, and some are starting to be closely related to epigenetic regulation by several mechanism (Wei et al. 2017).

Although it is true that epigenetic mechanisms act differently and have their own regulatory mechanisms, they are probably related to each other at some point to modulate the gene expression. They are essential in synchronizing biochemical and physiological mechanisms in growth, development, and reproduction in the plant cycle life. Recently, they are considered key in the strategies to deal with the sub or supra-optimal environmental conditions due to the changing dynamic of epigenetic marks, considering that stress and

environmental stimulus can induce epigenetic variation in the genome. This leads to phenotypic plasticity, the rising of alternative phenotypes expressed by the same genome, which is explained by alterations in the epigenetic marks in the genome to enhance the transcriptional regulation associated with the specific needs of plants according to the environment leading to acclimation (Asensi-Fabado et al. 2017; Fortes and Gallusci 2017) (Fig. 2A, B). An example of this phenomenon is the phenotype of clones of potatoes growing in 1000 m of altitude difference, in wherein the higher spot the plant had thicker leaves, shorter rachis, more tubers, and more anthocyanins, which were associated with the variability of epialleles, i.e. genetic loci that exhibit specific DNA methylation pattern (Ibañez et al. 2021). Similarly, *Potentilla saundersiana*, a rosacea plant, presented reduced biomass and height, smaller leaves, small stomatal aperture, cell wall thicker, skinnier vessels, and increased antioxidant system bioactivity compounds as a result of higher altitudes strategies to survive, all these phenotypes associated to epigenetic regulation and post-translational modification (Ma et al. 2015).

In nature, phenotypic plasticity is essential due to selective pressure on the population dynamics (Holeski et al. 2012). Indeed, the epigenetic variation depends partially on the same driving forces as a genetic variation but is more related to habitat conditions; such that epigenetic variation may be part of the natural selection, ecological interactions, and speciation process, and ultimately provide an accelerated way to evolutive changes (Parejo-Farnés et al. 2019). Two crucial aspects of plant behavior for plasticity are the learning process and memory, which require a continual perception of information from the environment and access to past experiences to incorporate the information in new responses (Trewavas 2016) to impact the long-term and transgenerational adaptation (Mirouze and Paszkowski 2011). Stress memory is defined as the information retention of past stress events resulting in a modified response that can be used to endure recurring stress (Lämke and Bäurle 2017; Galviz et al. 2020). This modification can be changed in the speed of the response or the magnitude of the response (Baldwin and Schmelz 1996). The learning process of plants involved, on the one hand, increased metabolites levels, signaling molecules and transcription factors, and on the other hand, alteration of epigenetic marks to coordinated changes in gene expression pattern (Crisp et al. 2016; Lämke and Bäurle 2017; Weinhold 2018; Galviz et al. 2020; Perone and Martinelli 2020).

The memory can remain days to weeks or months for somatic memory, but it may be stable and inherited within offspring to one, two (intragenerational), or more stress-free generations (transgenerational) to increase progeny success (Crisp et al. 2016; Lämke and Bäurle 2017; Weinhold 2018; Galviz et al. 2020). The memory duration will depend on the

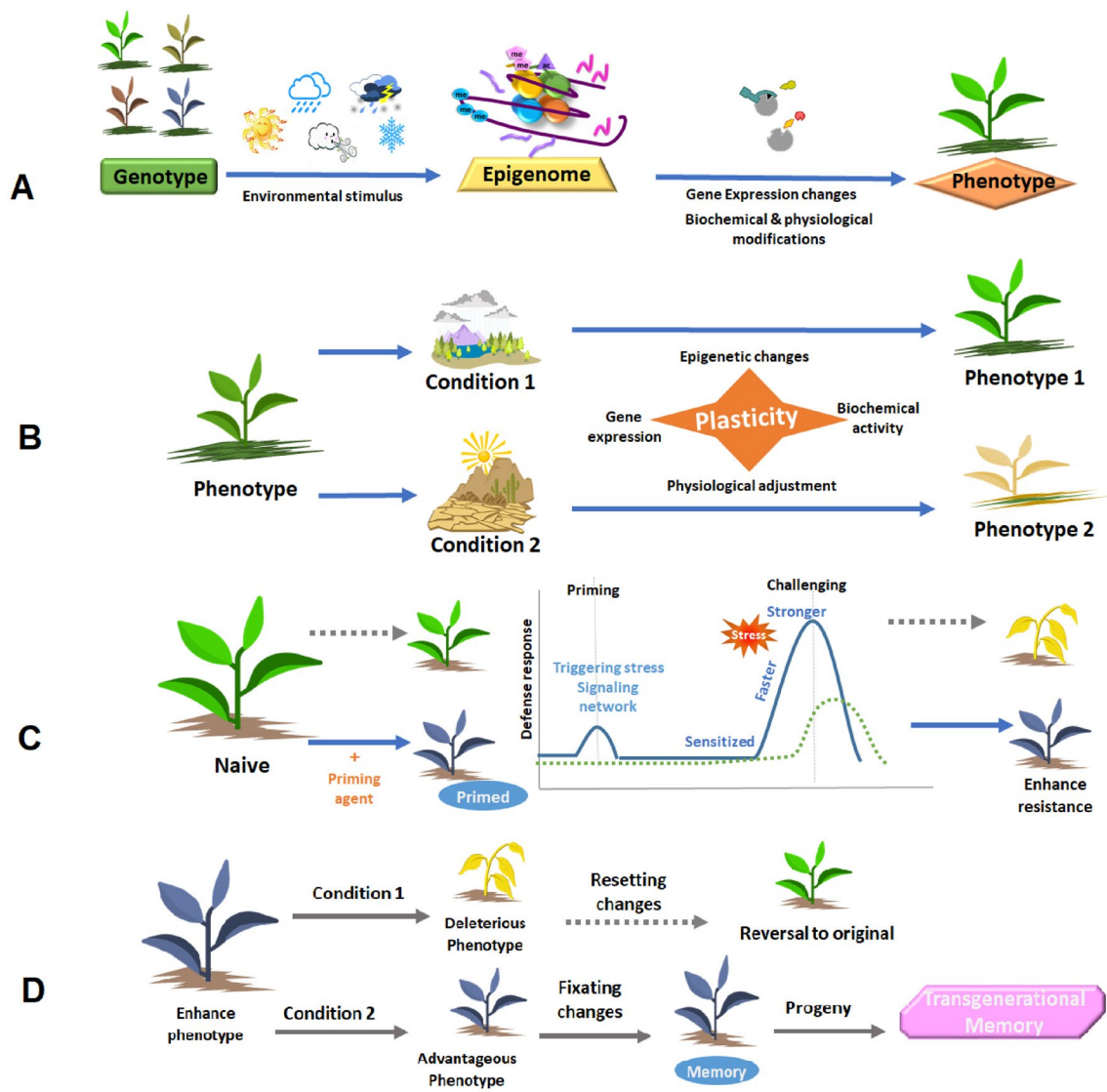


Fig. 2 Schematic concepts involved in the phenotype variation in an organism. **A** Phenotype determination. **B** Plasticity. **C** Priming. **D** Plant memory

stability of the epialleles responsible for the stress memory. They can be mitotically or meiotically stable. In the first one, the epigenetic state is maintained in the mitosis, such that the changes are persistent during vegetative growth but as a short-term inheritance throughout newly developing tissues and along the lifetime of the plant. In the second one, the epigenetic state can be transmitted through meiosis and gametogenesis, such that the effects on the phenotype are long-term and can be extended to the next generation (Deleris et al. 2016; Lämke and Bäurle 2017). As mentioned before, the phenotypic plasticity brought by a determined environment can aid in the survival of a population. However, after the recovery period, if the adverse conditions return to normal or change to another, considering that stress factors in nature could be transitory, some alternative phenotypes

can become deleterious for the individual (Fig. 2D). The reversibility of the epigenetic mechanism allows switching back to the initial state and reverting to the initial state of the original phenotype. Even when the phenotype plasticity is memorized and inherited to the next generations, it still exists the possibility of *resetting* and “forgetting” the altered responses leading to the re-appearance of the original phenotype if necessary. However, the molecular mechanism driving the learning, memory and forgetting process of plants is still unclear. Nevertheless, it is suggested that it may depend on the balance between the trade-offs involved in the process and the neutral, advantageous or disadvantageous effect according to the overall fitness of the individual (Burggren 2016; Crisp et al. 2016; Galviz et al. 2020).

A stress imprint can enhance beneficial memory or priming, which refers to a modified advantageous response, usually faster, stronger, and sensitized triggered by stress set up by previous stimulus and improved resistance to recurrent stress factors (Fig. 2C). When this occurs, the regulation network of stress-related genes is altered, and the plant is considered in a "primed state" (Crisp et al. 2016; Lämke and Bäurle 2017; Galviz et al. 2020). However, the priming agent, the first triggering cue, can be the direct exposure to stress or through applications of chemical, biological, plant hormone, or elicitor treatment (Avramova 2015; Crisp et al. 2016; Hilker and Schmölling 2019; Galviz et al. 2020; Turgut-Kara et al. 2020; Magno et al. 2021). In seeds, priming treatments are applied to hydrate the seed and improve germination (Ibrahim 2016), and several long-lasting effects persist in the plant life cycle, such as improving fitness and stress resistance (Bruce et al. 2007).

Priming could be applied at any developmental stage to improve tolerance exposure, in where the priming efficiency in generating a memory can vary according to the priming agent used; treatment duration, plant species, and seed primed storage. Although more studies are needed to apply to breeding programs, it is an interesting and potential approach to alleviate climate change impact on crops and improve agronomic traits. The use of eustressor as priming agents could be potential tools for crop management to generate a transgenerational memory and shape the stress tolerance in crops with a sustainable focus by enhancing the natural response innate ability of plants (Vázquez-Hernández et al. 2019).

Eustressors as stress resistance triggering allies

The preconditioning process implied in priming has as base the hormesis theory. This refers to a biological evolutionary theory that suggests that cells, organs, and organisms have a dose–response relationship to interact with environmental stressors and acclimate, such that low-dose stress may induce overcompensation responses, wherein occurs damage repair and adaptive background responses (Agathokleous and Calabrese 2019). In plants, it can promote growth, enhancing wound-healing capacity and secondary metabolite production to maintain homeostasis. The hormetic response is stress-dependent, such that it is classified in eustress and distress, according to the effect produced to plant, either beneficial or harmful, respectively (Vargas-Hernandez et al. 2017; Duarte-Sierra et al. 2020).

In this sense, it has been extensively pointed out that molecules that trigger or stimulate specific defense mechanisms in plants are called elicitors or stimulants (Malik et al. 2020; Iriti and Vitalini 2021), such that they can induce eustressic

responses in plants at low doses (Duarte-Sierra et al. 2020). Depending on the stress factor, dose and application opportunity can significantly induce plant immunity (eustressic dose) or improve plant growth and development (biostimulants). Recently, it has been proposed to define any inductor of a positive response like enhancing biological functions, productivity, and activation of defense pathways as a eustressor (Vázquez-Hernández et al. 2019).

The pre-exposition of plants to treatment with chemicals mimic endogenous stress signals leading to the activation of the defense mechanisms in the cells to prepare to affront the danger through their systemic acquired resistance (SAR) or induced systemic resistance (ISR) (Avramova 2019). Elicitors can activate defense mechanisms on the surface of the plasma membrane as induction of pathogenesis-related proteins and enzymes of oxidative stress protection and hypersensitive responses (Baenas et al. 2014). Early plant defense responses arises an ion flux (Cl^- , K^+ , Ca^{2+}), followed by reactive oxygen species (ROS) and reactive nitrogen species (RNS) production, which triggers downstream mitogen-activated protein kinases (MPKs) accumulation and stimulates hormones (SA, ABA, and JA) signaling pathways (Pastor et al. 2013). All these processes lead to the activation of transcriptional factors (TF), signaling proteins and later, the regulation of specific gene expression. At the functional level, the secondary metabolites production, oxidative stress protection synthesis enzymes, induction of pathogenesis-related proteins, and the reinforcement of structural and defensive barriers as well as the hypersensitive response are induced (Baenas et al. 2014). In primed mother plants stressed can occur the accumulation in seeds of the compounds above mentioned, and even this response can be across several generations because priming might facilitate transcriptional induction of defense genes and remain in the following generations if epigenetic changes occur (Pastor et al. 2013; Crisp et al. 2016). These may occur after the recovery process, fixing some responses to develop memory in plants (Lämke and Bäurle 2017), considering that epigenetic memory must exceed the duration of the original stimulus that established them and must have an impact on the subsequent gene expression (Avramova 2019). Hence, for the active use of eustressors in agriculture, it is desirable to focus on stress factors used in eustressic dose to favour a priming memory through epigenetic influence or has probed to show positive inter or transgenerational effects.

Epigenetic alterations by eustressors and possible stress memory triggering

Recent evidence suggests that epigenetic mechanisms are closely related to the fine-tuning control of all the biological processes occurring in an organism, considering they

modulate the expression of genes involved in primary metabolism and stress-related genes, such as they are essential for the acclimatization and adaptation in plants. Moreover, the elements involved in the metabolism of DNA methylation and histone PTMs are regulated by interactions with reactive oxygen species (ROS), nitric oxide (NO) and antioxidant compounds (Lindermayr et al. 2020; Saravana Kumar et al. 2020).

For instance, DNA methylation is involved in the regulation of the phenolic acids biosynthesis, as suggested in the experiment by Yang et al. (2018), in where the treatment with 5-AzaC (5-Azacytidine), DNA methylation inhibitor, and SAM (S-Adenosyl methionine), methyl donor, affected the phenolic acids production in *S. miltiorrhiza*. In the case of 5-AzaC, it induced the expression of genes involved in the two pathways of phenolic acids (phenylpropanoid and tyrosine-derived) and, accordingly, the concentration of phenolic acids. Additionally, it altered the methylation pattern of RAS promoter, inhibited the expression of genes involved in DNA methylation, as MET, and increased those involved in DNA demethylation, as MDB. On the contrary, with the SAM, these were opposite. It suggested that DNA demethylation is a negative regulator of phenolic acid biosynthesis (Yang et al. 2018). Other interesting findings come from sequencing experiments, as Zuo et al. (2017). In this, transgenic tomatoes to the ethylene response factor (ERF1), a regulator in ethylene-responsive genes, revealed several differential methylation regions in several genes involved in the ethylene (ETH) synthesis and signaling pathway. Additionally, miRNA target genes were found, which showed the interconnection in the DNA methylation and miRNAs co-regulation (Zuo et al. 2017).

Currently, increasing evidence suggests that epigenetic mechanisms are intricately linked with the modulation of phytohormones in plants, and vice versa, because hormones can affect the epigenetic state of the plant. ETH and jasmonic acid (JA) induce the expression of histone deacetylases HDA6 and HDA9, and on the contrary, the knocking out of these deacetylases provokes ABA hypersensitivity. This is through the interaction with transcription factors and associated proteins (Yamamuro et al. 2016). Similarly, multiple components of the auxin-signaling pathway are under the control of miRNAs that target auxin-related genes and transcription factors and genes controlled by dynamic changes in DNA methylation and histone modification levels. For this reason, epigenetic may be essential in the regulatory mechanism of hormone actions and, by consequence, in the stress networks in plants (Yamamuro et al. 2016).

As mentioned above, several studies have reported changes in the DNA methylation status and histone PTMs in specific genes by the exposure of plants to stress factors as drought (Fang et al. 2014; Kaur et al. 2018), cold (Pavangadkar et al. 2010; Tang et al. 2018), salinity (Sokol et al. 2007;

Yaish et al. 2018), high light conditions (Guo et al. 2008), depletion of nutrients as nitrogen and phosphorous (Mager and Ludewig 2018), contamination with heavy metals as cadmium (Xin et al. 2019), exposure to sulphur dioxide (Yi and Li 2013), physical wounding (Polkowska-kowalczyk et al. 2014), and pathogenic bacterial (Latrasse et al. 2017), viral (Wang et al. 2018), and fungus (Luo et al. 2016) infection. Equally, several miRNAs members have been described as functional in response to drought, pathogens (Yu et al. 2020), heavy metals like cadmium and aluminium, and activating plant immune response by pathogen-associated molecular patterns plant–microbe interactions (Huang et al. 2019; Sáenz-de la et al. 2020). Some miRNAs are involved in multiple stresses (Wang et al. 2017), and in others, their expression pattern varied in a species-specific manner (Álvarez-Venegas et al. 2016; Banerjee et al. 2017; Kumar et al. 2018). The epigenetic marks were correlated with activating stress-responsive genes or involved in the defense and immune response in all these cases.

The remaining question is about eustressors could induce an epigenetic pattern to trigger stress-stable tolerance without compromising the phenotype. A clear example is shown in the work by Cao et al. (2013), the H₂O₂ was tested as an elicitor against heat stress. The Methylation-sensitive amplified fragment length polymorphism (MSAP) analysis did not show significant differences in methylation levels between the treatments in this work. However, H₂O₂ led to changes in methylation status in some loci that alleviated the phenotypic damage caused by heat stress and altered the expression of some stress-responsive genes (Cao et al. 2013). Another interesting case is in the work by Kellenberger et al. (2016) is presented, in where MSAP of leaf damage by herbivory and treated with MeJA was compared. Both cases resulted in higher demethylation events in locus, mainly in the MeJA treated. However, in phenotype, the elicited plant did not show morphological changes but displayed lower volatile compounds and less herbivory and attractiveness to pollinators (Kellenberger et al. 2016). Despite the studies focused on these quizzing are numerous, the evidence is still limited, and more when it comes to transgenerational memory experiments.

Therefore, the use of eustressors, with stable intra/transgenerational inheritance, in the fields or under controlled conditions levels might be a simple and elegant solution for resilient crop development. For field productions, this may presume that no antagonistic interaction occurs between spontaneous environmental stresses and the eustressors used. In addition, in some cases, the eustressor could not be a milder form of the same stress, as in the climate-related stresses, but a chemical or biological eustressor treatment might induce some beneficial traits. For instance, phytohormones are emerging as potential priming tools for mitigating negative effects on plants by abiotic

stress (Rhaman et al. 2020). Even though the abiotic stresses more studied are temperature, drought and salt stresses, strengthening plants against heat stress could be achieved by a mimetic in a specific condition to effectively prime the plant (Magno et al. 2021), considering that it implies a different type of hydric stress pressure on the system. However, this approach needs much more development to define the application criteria to obtain the characteristics of interest. In Table 1, there are described some examples of studies wherein eustressors treatment suggested memory induction in the offspring.

As mentioned before, the study cases of transgenerational inheritance of stress resistance are limited. In Table 1, it is shown that in most cases, the inheritance is just examined in the next generation, being considered as intragenerational memory. In these cases, transgenerational stability is unknown. The study of cases where two or more generations are considered will be necessary to improve our insight about the correct memory induction for transgenerational stability. By mention, even when an enhanced stress tolerance is achieved and inherited to the next generation, the stress memory is erased in the second generation (Luna et al. 2012; Slaughter et al. 2012), or the memory partially remains in the second generation (Migicovsky and Kovalchuk 2015; Martínez-Aguilar et al. 2016; Ramírez-Carrasco et al. 2017; Cong et al. 2019). It is pointed out that memory creation is stochastic and conditional rather than a general response. It occurs when new homeostasis is reached, considering it depends on the trade-offs between growth and development against the potential benefits (Crisp et al. 2016). However, probably, the intensity of the stress or stimulus and time of development stage in the plant to exposure are critical to determinate efficiently the transgenerational memory (Reza Rahavi and Kovalchuk 2013). In addition, there must be considered the plant growing conditions to determine effective priming, or if need it, the more favourable conditions to fix the traits of interest (Magno et al. 2021).

There are two possible factors to determine memory creation: duration of the exposure and intensity of the stress. A long exposure could induce widespread, locus-specific epigenetic alterations that remain stable, so different stress levels could lead to different levels of stress memory (Lukić et al. 2020). In addition, it is possible that when the stimulus that originated the memory is more involved in the primary functions, as in the case of the N-deficiency, the benefits super pass the cost, and the process of stable memorizing could be preferred until the third stress-free generation after one long-stress (Kou et al. 2011).

The point of decision between remembers or forget relies on the balance of trade-offs, benefits, and costs in each case, and it occurs during the stress recovery period. On the one hand, memory fixation may offer protection against future stress and acclimation to changing environments.

Acclimation refers to the capacity of short-term responses of one organism to environmental changes through gene expression, developmental, morphological, and physiological adjustments to survive and extend its tolerance ranges. The acclimation can occur at early development stages and persist on the adult stage, or as reversible plasticity during the lifetime (Ashe et al. 2021; Pazzaglia et al. 2021). However, the process requires resource-intensive costs that may delay growth, development, yield, and risk of adaptive memory. On the other hand, resetting, even if it sustains the susceptibility to severe or recurrent stress with risk of fatality, maximizes growth under favourable conditions, increases yield, and avoids deleterious effects in the long-term of maladaptive memories (Crisp et al. 2016). It becomes a balance between the optimization of the parental against the fitness and survival of the offspring when it is difficult to predict specific types of stress that occur in the following generation to determine the best choice. Moreover, even though factors that are most likely to affect the following generations as climate and soil properties changes, these memories may not necessarily mean physiological adaptation to these conditions since a transgenerational aspect could increase seed dormancy to wait for more favourable conditions (Racette et al. 2019). The fixation of epigenetic marks enhancing acclimation could be considered a rapid adaptation due to the contribution to accumulated memory mechanism and altering plant-environment interactions. Adaptation implies a process of natural selection of better-suited genotypes to a new environment at the population level (Ashe et al. 2021; Pazzaglia et al. 2021).

An early epigenetic change (DNA methylation and histone PTMs reprogramming) could allow survival through plasticity following the stress. Nevertheless, these variations would accumulate after the phenotypic fitness given by epigenetic modification exceeded the one by genetic variation (mutations, genetic recombination). However, the phenotypic alteration may not be visible until the accumulation of genetic mutations. Stress-induced changes of epigenetic variation may be visible in the first generation, but, lately, there could be reset in the next generations. Therefore, the dual inheritance of genetic and epigenetic variation ensures adaptation (Tricker 2015).

The epigenetic memory can promote the adaptation to specific stress. However, more than the adaptation to a specific stress, the potential and the desired goal is to induce a memory with a broad-spectrum-resistance that includes multiple stress factors, considering the crosstalk in the network signaling stress responses. In nature, just one stress factor is almost non-existent, and the general condition is to have multiple factors in where the interaction of these determines the effect in the plant, so it is possible to develop a cross-tolerance to several factors related (Locato et al. 2018; Chang et al. 2020). Eustressors are probably more promising

Table 1 Study cases of intra and transgenerational memory induced by eustressors treatment

Eustressor	Specie	Stress tested	Changes	Reference
<i>BABA</i> (β -aminobutyric acid)	Potato	Pathogen resistance: bacteria	General hypermethylation state in the genome. DNA hypermethylation on R3a promoter after primed. It promoted the R3a upregulation at gene expression and infection resistance (F0) at pathogen challenge. Progeny presented less methylation, but higher R3a transcription, associated with enhanced transcription of SA-dependent genes (<i>NPR1</i> , <i>SiWRKY1</i> , <i>PR1</i>) and intergenerational resistance (F1)	Kuźnicki et al. (2019)
<i>BABA</i>	Potato	Pathogen resistance: Oomycete:	Deposition of histone marks: H3K4me2, H3K27me3, and H3K9me2 in <i>NPR1</i> and <i>SM1</i> genes. Higher expression of <i>PR1</i> and <i>PR2</i> genes (F0). Heritability of H3K4me3 mark in progeny (F1) and intergenerational resistance	Meller et al. (2018)
<i>BABA</i>	Common bean	Pathogen resistance: bacteria	Changes in H3K4me3 and H3K36me3 marks promoters of defense-associated genes by priming enhancing diseases resistance Increased <i>PR1</i> gene transcription after primed (F0) and continuously challenged by infection challenge in F1 and F2 kept the memory. Inducible-high expression of <i>WRKY29</i> and <i>PR4</i> genes in F1. Transgenerational resistance (F2) even if plants experience a stress-free generation	Martínez-Aguilar et al. (2016), Ramírez-Carrasco et al. (2017)
<i>BABA</i>	Arabidopsis	Pathogen resistance: bacteria	It was increased the <i>PR1</i> gene transcript level in the progeny (F1 and F2). Transgenerational enhance resistance. Additional treatment in F1 increased priming capacity. Second generation, without additional priming in F1, reverted to a susceptible phenotype	Slaughter et al. (2012)
<i>Cauliflower mosaic virus DNA (CaMV)</i>	<i>Brassica rapa</i>	Pathogen resistance: fungus	Parental primed plants (F0) and progeny (F1) displayed pathogen resistance. Progeny presented differential transcriptomic profile enhancing defense pathways (glucosinolate, flavonoid, and fatty acid biosynthesis)	Kalischuk et al. (2015)
<i>Saccharine & acibenzolar-S-methyl (ASM)</i>	<i>Barley</i>	Pathogen resistance: <i>Fungus</i>	Plants primed (F0) and progeny (F1) exhibited infection resistance with both treatments. However, treatment with ASM reduced germination. Growth rate unaffected	Walters et al. (2012)

Table 1 (continued)

Eustressor	Specie	Stress tested	Changes	Reference
<i>PstDC3000</i> (<i>Pseudomonas syringae</i>)	Arabidopsis	Pathogen resistance: bacteria	General DNA hypomethylation change Stronger induction of <i>PR1</i> gene in progeny (F1) remains over one stress-free generation (F2). The suggested intensity of stress is proportional to the durability of resistance. Enrichment of H3K9ac and H3K27me3 in <i>WRKY6</i> and <i>WRKY53</i> genes	Luna et al. (2012)
<i>Melatonin</i>	Wheat (<i>Triticum aestivum</i>)	Cold	Activation of <i>CBF</i> genes (related to cold stress signaling) and <i>ZAT10</i> and <i>ZAT12</i> (key activators of transcription of antioxidant genes related to ROS)	Li et al. (2018)
<i>ASM</i>	Common bean seeds	Pathogen resistance: bacteria	Progeny of primed plants (F1) reduces disease by 11%, and when treated again with ASM, the resistance increased to 60%, suggesting that additional stimulation provides an advantage for priming	Akköprü (2020)
Salt	Arabidopsis	NA*	Progeny of stressed plants (F1) showed a hypermethylation state in gene promoters with expression changes. It also correlated with enrichment of H3K9me2 and depletion of H3K9ac marks at methyltransferases genes	Bilichak et al. (2012)
N-depletion	Rice	N-deficiency	Detection of 11 locus-specific methylations in MSAP sites on stressed plants (S0), which 50% remained stable in the next 3 non-stressed generations (S1, S2, S3). The progenies showed enhanced tolerance to N-deficiency-stress, demonstrating acquired adaptative traits in plants	Kou et al. (2011)
Drought	Arabidopsis	Drought	Identification of 40 DNA methylation epialleles drought-associated, which did not correlate with responsive gene-expression changes. The only evidence of transgenerational memory was increased seed dormancy However, over six generations under repeated stress, the variability in methylations patterns was stochastic	Ganguly et al. (2017)
Drought	Wheat	Salt stress	The first generation (F1) had better tolerance to salt stress reflected by a 28% highest yield, improved leaf area, water relations, and osmolytes accumulation	Tabassum et al. (2017)

Table 1 (continued)

Eustressor	Species	Stress tested	Changes	Reference
Heavy metals	Rice	Heavy metals	There was identified three patterns of seven gene expression according to the induced gene expression changes: Hg (83%), Cu/Cd (72%) and Cr (66%), which correspond to inheritance, reversal to the basal and adaptation in the next generations S1 and S2. Changes associated with DNA methylation state of Tos17 retrotransposon	Cong et al. (2019)
Heavy metals	Arabidopsis	Exposure to Ni ²⁺ , Cd ²⁺ , and Cu ²⁺	Progeny of stressed plants (S1) exhibited an increased rate of recombination. When progeny was propagated without stress, it reverted to normal levels. However, when exposed to stress for five consecutive generations (S1 to S5), the recombination frequency remains high. Progeny also displayed tolerance to NaCl and methyl sulfonate	Rahavi et al. (2011)
UV-C, heat, cold	Arabidopsis	UV-C, heat, cold	Progeny of stressed plants (S1) improved the stress responses. It was observed that stress in early development is beneficial on seed size and responses, but mild stress exposure favors memory. However, severe stress at late development is negative, with lower tolerance	Reza Rahavi and Kovalchuk (2013)
Leaf damage	<i>Mimulus guttatus</i>	NA*	Progeny of damage parents (S1) presented increment in CG and CHG methylation variability. There were identified DMRs, in which CG tend to overlap with differentially expressed genes and CHG and CHH with transposable elements. It suggested that differential methylation is a mechanistic component of transgenerational plasticity	Colicchio et al. (2018)
Cold	Arabidopsis	Cold	Decrease leaves under stress, earlier bolting time; re-activation of transposons in the next two generations under stress conditions	Migicovsky and Kovalchuk (2015)
Heat	Arabidopsis	Heat	Progeny of stressed plants presents hypomethylation and elevated transposon expression. Increased expression of HSA2 and reduction in MSH2, ROS1, and several SUVH genes, which correlate with histone marks	Migicovsky et al. (2014)

Table 1 (continued)

Eustressor	Specie	Stress tested	Changes	Reference
Heat	<i>Brassica rapa</i> L.	NA*	Differential expression and processing of non-coding RNA fragments involved in metabolism, the proton pump, ATPase activity, the antiporter activity, the mRNA decay activity, and epigenetic regulation in the heat progeny stress plants	Byeon et al. (2019)

*NA not apply. Studies in where a physiological stress tolerance test was not performed, just the molecular probes

as epigenetic memory inductor agents due to their impact on crosstalk in signal transduction pathways. As mentioned above, if the impact on plant physiology is critical for memory stability, the activation of multiple signaling networks could be a key point in the fine-tuning control of stress memory induction. As mentioned above, priming by one type of eustressor can sometimes enhance plant responses to other types of stress (called “cross-priming”) (Lämke and Bäurle, 2017). For instance, enhanced immunity to bacterial pathogens can be induced by treatments with moderate-high or low temperature or by moderate salt treatments, associated with epigenetic histone PTMs marks in H3K14ac, H3K4me2 and H3K4me3 (Lämke and Bäurle 2017). Moreover, histone H3K4 methylation is commonly correlated with different types of somatic stress memory (Lämke and Bäurle 2017).

The DNA methylation is pointed out as the more stable by their conservation in CG context during DNA replication. Recently it is suggested that balance in DNA methylation and demethylation pathways are essentials to preserve the transgenerational stability of the genome (Williams and Gehring 2017). Though, histone PTMs also can be maintained in replicating cells, as is the case of the H3K27me3 mark, which is essential for the inheritance of silencing memory for the transition to flowering in vernalization (Jiang and Berger 2017). As several studies have shown, they are involved in the priming process. It is important to consider the epigenetic mechanism as complementary to each other, where the presence of multiple epigenetic marks could increase the opportunity for long-term transgenerational memory.

Eustressors as plant breeding allies

Eustressors could be potential allies in stress management programs in agriculture in the near future due to their impact on the epigenetic plant state, and consequently, on plant fitness and stress responses. The transgenerational stress memory may induce a broad-spectrum tolerance against stress factors due to the overlap of signaling pathways, changes in expression of stress-related genes and miRNAs, as well as changes in DNA methylation and histone alterations in cells. As we mentioned briefly, there are many eustressors, which could trigger eustress conditions in plants. Nevertheless, the capacity to induce desirable traits with a stable epigenetic base is unclear for each eustressor, and probably the effects on the plant are eustressor- dependent and specie-dependent. The most promising and practical to be used in fields are the chemical compounds, mainly natural occurring metabolites. Between these, the reactive oxygen–nitrogen–sulphur species (RONSS) stand out as a key priming agent because of their role as a key messenger in the physiology, metabolism, and responses to stress, and the

crosstalk tolerance they could induce in plants (Locato et al. 2018). By mention, recent studies have highlighted the use of sulfur fertilization to enhance drought tolerance (Chowdhury et al. 2020; Farman et al. 2021; Shafiq et al. 2021) and heavy metal exposure (Ragab and Saad-Allah 2021) in crops through the regulation of the enzymatic antioxidant system and photosynthetic efficiency. These suggest a degree of priming additional to the biostimulants effect in the yield. In addition, they might interact with other major S-containing compounds involved in the epigenetic marks metabolism, such as the S-adenosyl methionine, which is a donor of the -CH₃ group necessary for the DNA methylation. Moreover, eustressors could play a critical function in regulating the epigenetic mechanisms in plants, considering various elements of the intermediary activities and enzymes involved in DNA methylation, histone PTMs, and other chromatin remodelling are mediated by redox metabolism as ROS and NO (Saravana Kumar et al. 2020).

To date, several studies have shown that the use of eustressors has a positive effect on plants. On the one hand, it might have a biostimulant effect, as it is a growth promoter leading to increased crop yield. On the other, an increase in the presence of bioactive compounds, which in turn can favour a better response, to stress in plants, even promoting immunity through a certain degree of tolerance or resistance to stress. However, the permanence of this type of effect due to eustressors has not been studied in subsequent generations (Vázquez-Hernández et al. 2019; Jamiołkowska 2020; Malik et al. 2020; Teklić et al. 2021). Therefore, more research is required on the eustressor-epigenetic topic. It is also essential to consider the priming agent, concentration, exposition time, doses, and application periods to generate the expected desired memory. The fixation of transgenerational stress memory into a plant is still a highly variable phenomenon among plant species and even distinct genotypes of the same species (Racette et al. 2019). In addition, the capacity of a plant to express primed resistance depends on multiple signal transduction pathways (Slaughter et al. 2012), in combination with time life-cycle, genome-size, levels in genome-wide DNA methylation, and type of stress according to the plant natural life history (Weinhold 2018), severity of the stress, environmental conditions, and plant species (Ramírez-Carrasco et al. 2017). Therefore, studies aiming at these questions are needed.

In the first stage, it is necessary to determine the specific conditions of treatment for each particular case, due to the effects on the plant can vary according to the eustressor type applied, the application way, dose, number of treatments and interval between them, as well as the physiological stage of the plant and even the plant species. In addition, it is crucial to consider that combining two or more factors can have an interaction (synergist additive or antagonist) effect and modify the response in the plant (Baenas et al. 2014). It is

then indispensable to identify the epigenetic alterations the eustressor induced, the impact on the phenotype, and the stability and heritability of the epigenetic marks for establishing an effective plant breeding strategy (Fig. 3A).

There has been mentioned that genome-wide manipulation of epigenetic marks holds promise in plant breeding. However, the translation to crops remains determined due to the severe vegetative and development alteration resulting from genome-editing technologies (Taagen et al. 2020). Indeed, the genome-editing tools are potent tools for site-specific epigenome editing and are more stochastic than the proposal of induction through eustressors. The side effects are more unpredictable in the first case as the molecular system is strained. In the second, the eustressor promotes a balance in the entire system before establishing epigenetic marks.

It is expected that eustressors become a tool that, together with traditional plant breeding techniques and genome-editing techniques, could take plant breeding to a new level. They have the potential to provide crops with broad-spectrum resistance to biotic and abiotic stresses to enhance phenotypic characteristic that allows the plants to cope with environmental conditions that, in another scenario, would cause severe damage, even death, and in consequence, yield losses. Additionally, if the eustressor induces specific epigenetic marks related to the adaptation to the environment, these characteristics may be conserved during the life cycle of the crop and if they are stable to be heritable, even though following generations (Fig. 3B). However, transgenerational stability becomes essential to determinate the re-application of the eustressor in the next generations and dose to keep the epigenetic marks stable and, consequently, the prolonged beneficial effects in plants and agronomic traits.

It is essential to maximize the phenotypic variations of resistance to stress, considering that overcoming climate change and growing population challenges is critical to the world population's wellbeing. We need to create a new approach based on the new knowledge of the mechanism of plant response to stress and adaptability to a defiant environment. The use of eustressors combined with epigenetic regulation could stand as high potential in future agricultural systems due to their advances to the plant and the farmer (Fig. 4). It could be a time and cost-effective method, considering that eustressors are used at low concentrations to trigger the desirable effect; a higher concentration can be harmful to the plant, which means a low cost. Additionally, depending on the eustressor, some of them can be easily applied in the field conditions as part of the irrigation system or in foliar spraying, even as a seed priming before sowing (i.e. phytohormones, plant growth-promoting bacteria, acoustic waves traveling in the irrigation system, etc.). In the case of other types of eustressor as some physical factors, they could be treated by mimetic agents or directly through

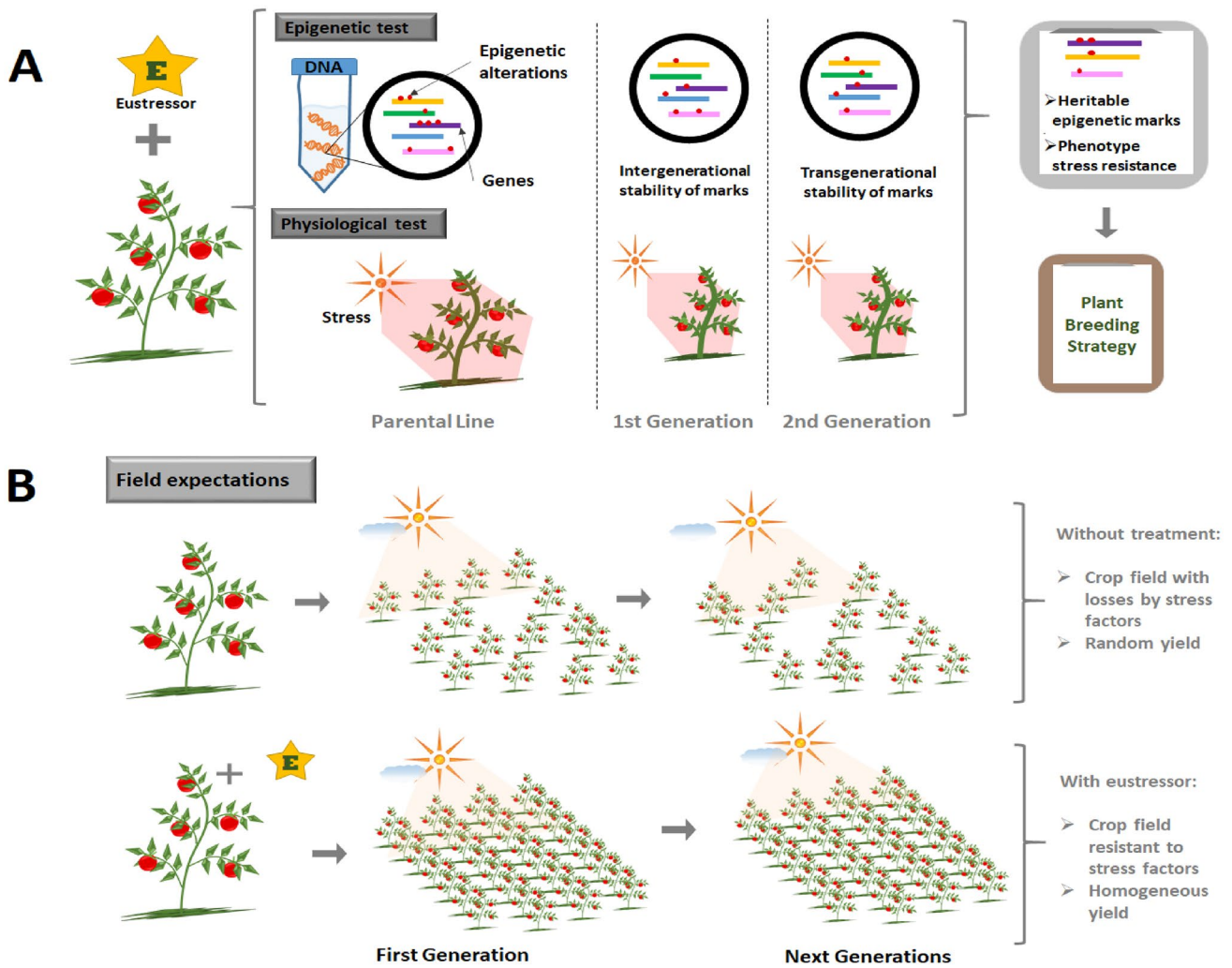


Fig. 3 Eustressors perspectives in agriculture. **A** Eustressors-epigenetic investigation process: the eustressor is tested in the plant at the physiological level (resistant phenotype) and epigenetic level (identify epigenetic alterations related to the desirable traits and their sta-

bility across generations) to determinate a plant breeding. **B** Field expectations of eustressor use: crop with resistance to the occurrence of environmental perturbations without yields reductions

strategies in seeds or seedlings before planting. The application of eustressors in general terms and most of the cases do not require specialized equipment and can be implemented in any production system.

Moreover, they could be innocuous to the environment, the users, and the adjacent organism, due to eustressors are expected to be much less toxic than agrochemicals (Iriti and Vitalini 2021). This is a favourable point since it is compatible with the sustainability objectives intended for agriculture in the coming decades. From the plant point of view, the eustressors allow conserving the genetic pool diversity of the population. However, it may only enhance epigenetic diversity selection, which in case it is not convenient or valuable to the plant fitness, it could be reverted to its original state. However, thinking in the resistance stress trails, the outcome will be favourable to generate a

stable memory in the crop, which will improve the productivity and the quality of agricultural products (Tirnaz and Batley 2019).

To date the understanding and application of epigenetic and stress memory in breeding strategies are limited, but they have a great potential for improving crop varieties through the production of new epialleles to controlling gene expression during development in response to the environmental pressure (Kakoulidou et al. 2021; Sun et al. 2021). There are still challenges to reach regarding the use of stressor for fix characters of interest through memory, as plant and conditions specific protocols based on desirable goals, such that further research needs to be performed to elucidate the missing gaps to design suitable strategies, opening new fields of research as the primeomics (Srivastava et al. 2021).

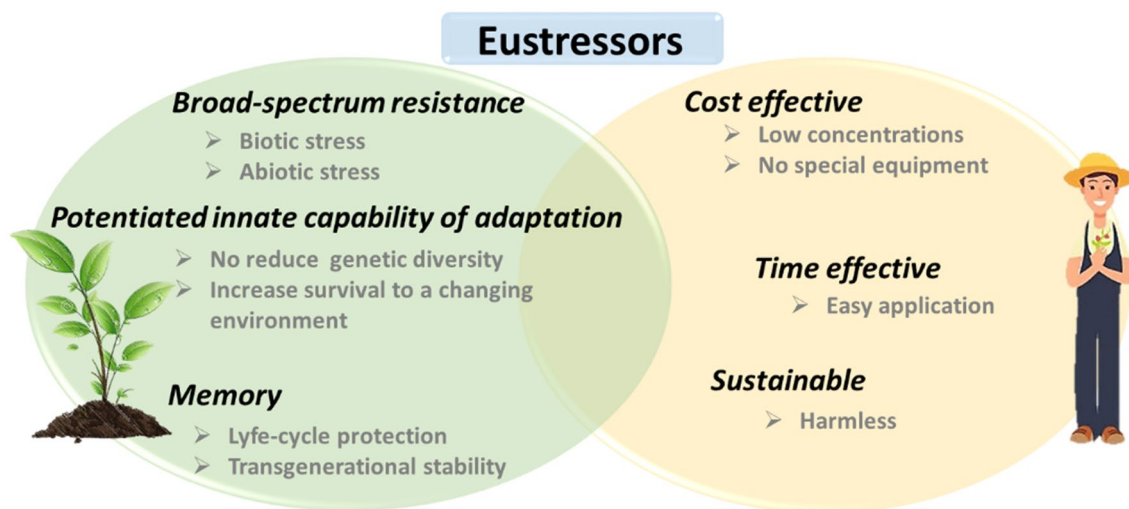


Fig. 4 Eustressors advance in plant breeding. Advances that made the eustressors a potential tool to be implemented in plant breeding. It includes the plant benefits induced by the eustressor as the broad-spectrum resistance to stresses, the potentiation of their capability of

adaptation and memory creation, and the agriculture profits of use eustressor as could be the cost and time effectiveness and sustainability

Concluding remarks and perspectives

Eustressors have a critical impact on the physiology, biochemistry, genetic and epigenetic of plants, making them a powerful tool to use in agriculture to enhance the adaptation of crops to a changing environment. However, further research needs to be carried out to solve transgenerational memory establishment and stability through eustressors and its effects on desirable plant traits for plants adaptation to stress, and therefore use it wisely. There are many questions to answer: what is the ideal stimulus and dose to induce memory? Is it the same effect one long against multiple short stimuli? How many stimuli are necessary? How long can the memory remain in the descendants? These and other questions will be answered with future research in the field. Besides, once knowledge of transgenerational stability with elicitors is sufficient, it will be necessary to generate a broader epigenetic background in the germplasm of agronomic interest species to induce controlled changes useful for plant breeders. It is also important to mention that the controlled elicitation to induce transgenerational epigenetic changes does not replace traditional plant breeding practices. Eustressors used in a controlled manner during plant cultivation are a potential tool to decrease the time and cost of selecting resistant crop varieties when climate change and accelerating population growth make it indispensable to improve world food security.

Acknowledgements ALVA thanks the Consejo Nacional de Ciencia y Tecnología (CONACYT) for providing the Postgrad Scholarship (No. 714246). RGGG also acknowledges the SEP-CONACYT Basic

Science 2016 (No. 283259) for supporting this work. Apologies to all researchers whose works could not be cited in this paper. In addition, special acknowledges to the reviewers of this paper for taking the time to provide valuable feedback to improve the article.

Author contributions ALVA did the literature research and draft preparation. RGGG directed the manuscript. All the authors have read and approved the final manuscript.

Funding Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication All the authors agree with the publication of the manuscript.

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