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Review article

Herbicide resistant weeds: A call to integrate conventional agricultural practices, molecular biology knowledge and new technologies

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ABSTRACT

Herbicide resistant (HR) weeds are of major concern in modern agriculture. This situation is exacerbated by the massive adoption of herbicide-based technologies along with the overuse of a few active ingredients to control weeds over vast areas year after year. Also, many other anthropological, biological, and environmental factors have defined a higher rate of herbicide resistance evolution in numerous weed species around the world. This review focuses on two central points: 1) how these factors have affected the resistance evolution process; and 2) which cultural practices and new approaches would help to achieve an effective integrated weed management. We claim that global climate change is an unnoticed factor that may be acting on the selection of HR weeds, especially those evolving into non-target-site resistance mechanisms. And we present several new tools –such as Gene Drive and RNAi technologies- that may be adopted to cope with herbicide resistance spread, as well as discuss their potential application at field level. This is the first review that integrates agronomic and molecular knowledge of herbicide resistance. It covers not only the genetic basis of the most relevant resistance mechanisms but also the strengths and weaknesses of traditional and forthcoming agricultural practices.

1. Introduction

One of the main issues in modern agriculture is the ever-increasing occurrence of herbicide resistance in weeds. From an agronomic view, herbicide resistance can be defined as the inherited ability of a plant to survive and reproduce after the exposure to a dose of herbicide that is normally lethal to a wild-type plant of the same species [1]. This dynamic process impacts on both crop production and the environment, and it represents a major challenge to farmers, scientists and the agribusiness sector.

The use of herbicides has been the main –almost exclusive– tool used for weed control worldwide since the late 1960s. However, the continuous use of the same herbicide or of herbicides with the same mode of action (MOA) has inevitably led to the selection of resistant weed populations [2]. Furthermore, during the last two decades, the extensive adoption of transgenic crops tolerant to herbicides such as glyphosate has led the agrochemical industry to slow down the development of new herbicidal molecules, particularly those with new MOAs [3]. Rapid efficacy combined with operative simplicity has resulted in the overuse of a small number of herbicides, favoring the selection of resistant weeds, mainly in the United States, Australia and South America. The situation is also a concern in the European Union, where the adoption of conventionally bred herbicide-tolerant crops has led to wide spread instances of herbicide resistance [4].

There are many factors influencing the resistance evolution process, and they can be broadly classified into two groups: anthropological and biological. The anthropological factors are those related to human interventions and weed management agronomic practices. These include the use of different herbicides, the number of applications over time along with their in-field application doses, as well as the selection of crops and pastures for rotation, and the use of grazing animals and tillage practices [5,6]. The biological factors include ecology, genetics, the life history of every weed species, and the resistance mechanisms involved.

There are two broad types of resistance mechanisms: target-site and non-target-site. Target-site resistance (TSR) occurs when herbicides

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reach the target site at a normally lethal dose, but their impact is limited by the site's changes; while non-target-site resistance (NTSR) involves mechanisms that either minimize the amount of active herbicide reaching the target site or protect the plant against oxidative damages from herbicide action [7–9]. Both resistance mechanisms can be caused by structural or regulatory mutations [8]. In the first type, changes in a protein-coding DNA sequence modify the 3-dimensional structure of the herbicide-targeted protein, which lowers herbicide efficiency. The second type of mutation results in the differential expression of one or several genes in resistant plants compared to sensitive plants, and it includes whole-gene amplification, changes in the promoter sequence and epigenetic processes (e.g., DNA methylation).

During the last decade, omics has begun to contribute significantly to decoding the molecular mechanisms of herbicide resistance. In particular, comparative genomics is helping to identify the genetic basis of weedy traits [10]. Likewise, RNA-seq studies provide a deeper understanding of the molecular basis of non-target-site resistance, especially in those species with little or no previous sequence information [11]. The integration of different omics is crucial to achieve a broader comprehension of the biological systems that may impact the development of future weed management strategies.

Overall, this work aims to discuss the current global status of HR weeds, by focusing on three central points: i) the molecular basis of herbicide resistance known until now; ii) the factors that have affected the resistance evolution process; and iii) the control strategies that would help to achieve an effective integrated weed management, considering both traditional agronomic practices and newly emerged technologies. This review integrates the main agronomic components with the molecular biology knowledge of herbicide resistance, evidencing a huge demand for new research in this still underexplored interaction.

2. Herbicide resistance mechanisms

2.1. Target-site resistance evolution: a bit of history

Target-site resistance (TSR) mechanisms were the first to be elucidated. The first serious case of TSR was documented in 1968 in a common groundsel (*Senecio vulgaris L.*) population that was no longer controlled by simazine or atrazine [12]. Specifically, the triazine resistance mechanism was due to a mutation in the chloroplast *PSBA* gene, changing serine 264 to glycine, which reduced the affinity of D1 protein in photosystem II for triazine herbicides [13].

However, it was not until the 1980s that cases of herbicide resistance became widespread. These involved inhibitors of acetyl coenzyme-A carboxylase (ACCase) and acetolactate synthase (ALS) [14]. Resistance to either was caused by target site mutations, in both cases acting as a functionally dominant traits. Several cases evolved quickly in multiple species [15,16] as a consequence of the limited fitness costs associated with these resistance traits [9]. Additionally, in contrast to the first detected TSR to triazine that was only maternally inherited [17], ALS and ACCase inhibitor mutations are also paternally inherited, allowing for spread of resistance mutations via pollen.

In 1996, glyphosate resistant (GR) crops were introduced to North and South America, and later, to Australia. Some cases of GR weeds started to be reported soon afterwards [18,19]. The point mutation in a key residue (proline 106) of the 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS; glyphosate's target protein) confers weak resistance to glyphosate [20]. Another TSR mechanism, which involves the overexpression of EPSPS by gene amplification, was reported in several GR weeds [21–24]. The genomic mechanisms causing this gene amplification include both tandem gene duplication [25,26] as well as the proliferation of an extrachromosomal element [27]. These mechanisms are associated with transposable elements, which are hypothesized to play a role in the formation of duplicated gene copies. Additionally, the double amino acid substitution in the EPSPS -called TIPS- has been reported in *Eleusine indica* [28,29] and *Bidens pilosa* [30]; while a new double mutation -called TIPT- [31] and a novel triple amino acid substitution -called TAP-IVS- [32,33] have been recently characterized in *Bidens subalternans* and *Amaranthus hybridus*, respectively.

For some herbicides, TSR mechanisms have evolved in relatively few species, especially for to those herbicides that are not widely used [34]. This makes sense if we consider that a high selection pressure is the main force that drives resistance spread, although this explanation would also be valid for NTSR. However, in some cases, there are other reasons for this phenomenon to occur. For example, in the case of synthetic auxin herbicides, the low incidence of TSR can be attributed to the multiple sites of action they have (auxin receptors and auxin-specific transporters) and the functional redundancy in the receptor family [35]. As a consequence, only stacked mutations would significantly alter the response to these herbicides, but not without a concomitant fitness cost. There is only one case that confirms the evolution of TSR to synthetic auxins in *Kochia scoparia*, which involves the AUX/IAA co-receptor [36]. However, there are also other possible TSR cases (coexisting with NTSR mechanisms) in *Raphanus raphanistrum* [37] and grasses [38,39]. Specifically, the accumulation of cyanide that results from quinclorac-induced ethylene production has been proposed as the main mechanism of action of this herbicide in susceptible grasses [40]. An alteration in the induction of the ethylene biosynthesis pathway (more precisely, in the two key enzymes ACC synthase and ACC oxidase) seems to be involved in this resistance [38,39]. Nonetheless, the genetic basis of this apparent TSR remains unclear.

A singular TSR evolution is represented by the protoporphyrinogen oxidase (PPO) inhibitors. In this case, glycine 210 located near the active site of PPO is missing [41]. This deletion reduces herbicide binding efficiency while retaining enzyme activity. Computational models suggest that such deletion eliminates an important interchain hydrogen bond between glycine 210 and serine 424, resulting in a conformational change of the binding pocket and, thus, resistance [42]. This unusual TSR was confirmed in only two species: *Amaranthus tuberculatus* and *Amaranthus palmeri* [41,43] but recently, some other PPO point mutations have been found in the latter species [44,45].

Table 1 summarizes the types of TSR (and NTSR) mechanisms found in weeds thus far, which have evolved against the six most problematic herbicide groups.

2.2. Non-target-site resistance: a slower but persistent walk

Although the first case of NTSR was reported in 1957 in a 2,4-D resistant wild carrot (*Daucus carota L.*) population [46,47], only a few non-target-site mechanisms have been elucidated at the molecular level up to now [48]. This is because biochemical processes are inherently complicated and have a quantitative nature, and available genomic information for weedy species is limited. This polygenic nature of the NTSR mechanisms has a direct incidence on their evolution, as every gene provides some level of resistance. Thus, when a herbicide does not achieve full weed control in successive generations (usually because of a reduced application rate), then different NTSR genes might contribute to increase herbicide tolerance [49]. In outcrossing species, where individuals exchange and recombine alleles, NTSR development should be faster than in self-pollinated species. Additionally, how fast NTSR alleles accumulate in a population depends on their initial allelic frequency, the genetic diversity and population size, the selection pressure, and the resistance fitness costs [50].

Metabolic resistance is one of the best elucidated NTSR mechanisms, and can be described as a plant detoxification process that commonly consists of four phases [51–53]. We have summarized this process in detail in Fig. 1. Délye et al. [7] proposed that part of the NTSR may be constitutive and part could be induced because the plant detoxification process was under polyallelic genetic control. Recently, a comparative transcriptomic analysis has allowed the identification of

Table 1
Summary of the resistance mechanisms reported in weeds for the most used herbicide groups.

Herbicide Group[D]	Herbicide Resistance [B,C]			Ref.[A]
	Mechanistic and genetic basis	Molecular players	Physiological/biochemical effect	
	TSR, ACCase amino acid substitutions: **I1781**L/V/A/T; **W1999**C/L/S; **W2027**C; **I2041**N/V/T; **D2078**G; **C2088** R; **G2096**A/S	ACCase	Reduced herbicide sensitivity of ACCase	[15,85]
	TSR, *ACCase* gene overexpression?	ACCase	Higher ACCase activity	[86–88]
	TSR, *ACCase* gene overexpression	ACCase	Higher ACCase activity?	[88]
	NTSR, unknown basis	Greater epicuticular wax density in the leaf cuticles	Reduced foliar absorption	[89]
	NTSR, unknown basis	Cyt P450	Enhanced metabolism	[90–92]
	NTSR, unknown basis	Cyt P450; GST	Enhanced metabolism	[71,93]
	NTSR, gene overexpression: CYP72A; NMO; GT; GST	Cyt P450; NMO; GT; GST	Enhanced metabolism	[57]
	NTSR, gene overexpression: CYP87A3; CYP71D7; PIR7B; GDSL esterase/lipase 4g01130; Peroxidase (1, 66); GST (U1, U6, T3); UDP-GT (73C1,85A2); ABC transporter B family member 10	Cyt P450; esterase; POD; GST;GT; ABC transporter	Enhanced metabolism	[60]
	NTSR, gene overexpression: CYP71A4	Cyt P450	Enhanced metabolism	[61]
	NTSR, gene overexpression: AmGSTU1; AmGSTF1; AmGSTL1	GST	Enhanced metabolism and protection against collateral damage	[69,81]
B (ALS inhibitors)	**TSR,** ALS amino acid substitutions: **A122**T/V/Y/S/N; **P197**T/H/R/L/Q/S/A/I/N/E/Y/M/K/W; **A205**V/F; **D376**E; **R377**H; **W574**L/G/M/R; **S653**T/N/I; **G654** E/D	ALS	Reduced herbicide sensitivity of ALS	[9,16,94–96]
	TSR, *ALS* gene overexpression	ALS	Higher ALS activity?	[97]
	NTSR, unknown basis	Greater epicuticular wax density in the leaf cuticles?	Reduced foliar absorption	[98]
	NTSR, unknown basis	Cyt P450	Enhanced metabolism	[91,99]
	NTSR, gene overexpression: CYP71AK2; CYP72A254	Cyt P450	Enhanced metabolism	[59]
	NTSR, gene overexpression: CYP81A12; CYP81A21	Cyt P450	Enhanced metabolism	[100]
	NTSR, gene overexpression: CYP71A; CYP71B; CYP81D	Cyt P450	Enhanced metabolism	[58]
	NTSR, gene overexpression: CYP94A1; CYP71A4	Cyt P450	Enhanced metabolism	[61]
	NTSR, gene overexpression: CYP72A; CYP81B1;GST; GT	Cyt P450; GST; GT	Enhanced metabolism	[56]
	NTSR, gene overexpression: CYP96A13; ABCC1	Cyt P450; ABC transporter	Enhanced metabolism	[68]
	NTSR, gene overexpression: Esterase; GST (U1, U6); GT; POD (5, 65); CAT (1, 2)	Esterase; GST; GT; POD; CAT	Enhanced metabolism and protection against collateral damage	[72]
C (PSII inhibitors)	**TSR,** D1 protein amino acid substitutions: **L218**V; **V219**I; **A251**V; **F255** I/V; **S264**G/T; **N266**T	D1 protein	Reduced herbicide sensitivity of D1protein	[101–107]
	NTSR, gene overexpression: CYP?	Cyt P450	Enhanced metabolism	[108]
	NTSR, gene overexpression: AtuGSTF2?	GST	Enhanced metabolism	[70]
	NTSR, unknown basis	GST	Enhanced metabolism	[109]
	NTSR, unknown basis	Unknown	Reduced absorption and translocation	[110]
E (PPO inhibitors)	**TSR,** PPO G210 codon deletion	PPO	Reduced herbicide sensitivity of PPO	[41,43]
	TSR, PPO amino acid substitutions **R128**G/M; **G114**E; **S149**I; **G399**A	PPO	Reduced herbicide sensitivity of PPO	[111,44,45]
	NTSR, unknown basis	Cyt P450	Enhanced metabolism	[67]
	NTSR, unknown basis	Cyt P450; GST	Enhanced metabolism	[66]
F (synthetic auxins)	**TSR,** IAA16 amino acid substitution: **G127**N	AUX/IAA co-receptor	Altered auxin signaling	[36]
	TSR + **NTSR?,** gene overexpression: IAA29; IAA30; MEKK1; ABCB11	AUX/IAA co-receptor phosphorylated MAPK ABCB-type auxin efflux transporter	Altered auxin signaling, enhanced defense response and reduced translocation	[37,80]
	TSR + **NTSR?,** unknown basis	ACC synthase; ACC oxidase; β-cyanoalanine synthase	Alteration in the ethylene response pathway and protection against collateral damage	[38,39]
	NTSR, unknown basis	unknown	Reduced foliar absorption	[112]
	NTSR, unknown basis	unknown	Reduced translocation	[113,114]
	NTSR, gene overexpression: CHS	quercetin and kaempferol overproduced by chalcone synthase ABCB-type auxin efflux transporter?	Reduced translocation	[115]
	NTSR, unknown basis	unknown	Enhanced metabolism	[116]
	NTSR, unknown basis	Cyt P450	Enhanced metabolism	[62,65,117]

(*continued on next page*)

Table 1 (*continued*)

Herbicide Group[D]	Herbicide Resistance [B,C]			Ref.[A]
	Mechanistic and genetic basis	Molecular players	Physiological/biochemical effect	
G (EPSPS inhibitors)	**TSR,** EPSPS amino acid substitutions **P106**S/A/T/L; **T102**S	EPSPS	Reduced herbicide sensitivity of EPSPS	[20,118]
	TSR, EPSPS amino acid double substitution: **T102**I + **P106**S **T102**I + **P106**T	EPSPS	Reduced herbicide sensitivity of EPSPS	[28–31]
	TSR, EPSPS amino acid triple substitution: **T102**S +**A103**V +**P106**S	EPSPS	Reduced herbicide sensitivity of EPSPS	[32,33]
	TSR, ***EPSPS*** gene amplification (eccDNA)	EPSPS	Higher EPSPS activity	[27]
	TSR, ***EPSPS*** gene amplification (transposon-mediated tandem duplication)	EPSPS	Higher EPSPS activity	[26]
	TSR, ***EPSPS*** gene amplification (unknown genomic mechanism)	EPSPS	Higher EPSPS activity	[119,120]
	NTSR, unknown basis	Unknown	Reduced foliar absorption and translocation	[121]
	NTSR, unknown basis	Unknown	Reduced translocation	[48,73–76]
	NTSR, unknown basis	ABC transporter?	Reduced translocation	[122,123]
	NTSR, gene overexpression: M10; M11; M7; P3; ABCG29; ABCC3; ABCG42	ABC transporter	Reduced translocation	[78,79]
	NTSR, unknown basis	Unknown	Rapid cell death ('phoenix' mechanism)	[124]
	NTSR, unknown basis	Unknown	Enhanced metabolism	[125]
	NTSR, gene overexpression: CYP82D47	Cyt P450	Enhanced metabolism?	[126]

Abbreviations: ACCase: acetyl-CoA carboxylase; Cyt P450: cytochrome P-450; GST: glutathione-S-transferase; NMO: nitronate monooxygenase; GT: glycosyl-transferase; ALS: acetohydroxyacid synthase; POD: peroxidase; CAT: catalase; PSII: photosystem II; PPO: protoporphyrinogen oxidase; EPSPS: 5-en-olpyruvylshikimate 3′-phosphate synthase; eccDNA: extra-chromosomal circular DNA.

[A] Representative review articles and some of the most methodologically complete research articles were selected for each mechanism.

[B] Combinations of two or more mechanisms within each herbicide group have often been reported in a single population. However, multiple mechanisms were explicit only in cases where there are no reports of individual contributions to resistance.

[C] A question mark was added when a hypothesis without substantial empirical validation was proposed in the cited articles.

[D] Each mechanism is associated to resistance to either a single active ingredient, a complete chemical family, several chemical families or the whole herbicide group. For more detail, please refer to the cited articles.

several up-regulated transcription factors involved in stress response signaling and regulation in glufosinate-tolerant *A. palmeri* biotypes [54]. Although it can be expected that a coordinated regulation of detoxifying genes should confer herbicide resistance, there is a limited description of transcription factors involved in NTSR so far.

Since the activation of toxic molecules in phase I plays a crucial role

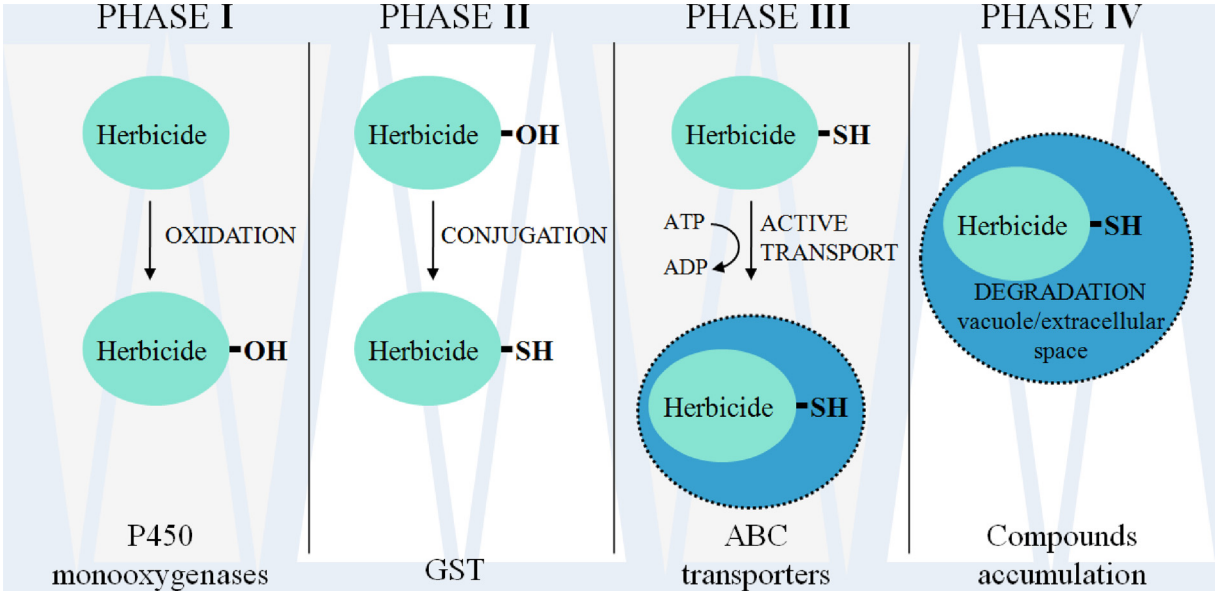

Fig. 1. Non-target-site herbicide resistance as a detoxification process that follows a four-phase schema.
Phase I comprises the activation step, where herbicide molecules are modified so that certain functional groups are exposed to the next step's enzymes. Usually, this modification is carried out by P450 monooxygenases or mixed-function oxidases. Phase II generally involves conjugation, which implies the binding of a bulky hydrophilic molecule to the activated herbicide through sugars or thiol groups. This process is mainly done by Glutathione-S-Transferases (GSTs), and it enables the recognition of the modified herbicide by the proteins of phase III. Phase III entails the active transport of the conjugated herbicide molecule into the vacuole or the extracellular space, commonly carried out by ABC transporters. Finally, in phase IV, the conjugated molecule is further degraded within the vacuole or in the extracellular space.

in further detoxification by enzymes in phase II (see Fig. 1), the initial characterization of metabolic resistance in any HR weed usually focuses on the identification of the cytochrome P-450 (cyt P450) involved in each NTSR case. Enhanced herbicide metabolism due to the altered expression of cyt P450 and other metabolism-specific genes have been mainly characterized in grass species, explaining how these species survive a wide range of herbicides [55–61]. However, many reports have confirmed that metabolic resistance can also be present within broadleaf weeds [62–68], although its genetic basis is underexplored. So far, glutathione-S-transferase (GST) and/or glycosyl-transferase (GT) induction has been confirmed to cause enhanced herbicide metabolism in both grasses and broadleaf weeds [56,57,60,66,69–72].

Another NTSR mechanism is the reduction in herbicide translocation, *i.e.* a restriction in herbicide mobility within the plant (via xylem and/or phloem) and/or its compartmentalization (sequestration in the cell wall or vacuole; active exclusion from the chloroplasts) [50]. Obviously, these mechanisms are mainly for systemic herbicides. For example, reduced glyphosate translocation has been documented in several GR populations [53,73–77]. Curiously, two studies reported the involvement of ABC transporters in vacuolar sequestration of glyphosate in *Conyza canadiensis* [78,79], but the candidate genes have not been functionally validated yet. Similarly, an ABCB-type auxin efflux transporter has recently been associated with 2,4-D resistance in *Raphanus raphanistrum* [80], although a subsequent transcriptomics study suggested that reduced translocation may not be as strong a resistance mechanism as originally thought [37].

For NTSR mechanisms involving reduced foliar absorption or protection against oxidative damage stemming from herbicide action, there are a few in-depth studies that point out the role of cuticular waxes and several detoxifying enzymes, respectively. Enzymes such as GST (considering its glutathione-peroxidase activity), catalases (CATs) and peroxidases (PODs) are considered essential against the oxidative damage induced by herbicides [69,72,81]. Moreover, elevated β-cyanoalanine synthase activity has been suggested as a mechanism contributing to quinclorac resistance in grasses by increasing the ability to detoxify cyanide [38]. Protection against oxidative damages has never been identified as an exclusive mechanism in a resistant population, probably because of its poor contribution to agronomic resistance.

Finally, an unusual NTSR case involving rapid cell death has been observed in GR populations of *Ambrosia trifida* [82]. Surprisingly, just a few hours after glyphosate spraying, the treated plant tissue withers and dies. Thus, the herbicide cannot be translocated from the dead zones, and plants can generate new organs through meristems. Although the molecular basis of this mechanism is still unknown, it has been found to trigger an increase in reactive oxygen species, to require light or exogenous sucrose, and to be inhibited by the addition of aromatic amino acids, suggesting that it might be associated with shikimate pathway inhibition [83].

Thus, while target-site gene mutations were evolving and were readily detected by weed scientists, the NTSR alleles were accumulating less noticeably. So, 'the rabbit and the turtle's fable' appears to have its version in the herbicide resistance evolution. Nowadays, increasing numbers of NTSR cases are being reported for the most important herbicide groups worldwide [7,9,84]. So, the turtle (NTSR) seems to be finally winning the race.

Table 1 summarizes all NTSR mechanisms detected up to now for the most commonly applied herbicide groups, reflecting the deepest knowledge achieved in each case.

3. How can the knowledge of population genetics contribute to management decisions?

The development of effective weed control strategies requires an extensive understanding of each weed population. This includes knowledge of flower biology and reproductive systems, fecundity, variations in seed dormancy, seeds and pollen migration distances, and the benefit/cost balance for the maintenance of genetic polymorphism. Furthermore, elucidating resistance mechanisms at the molecular level (target and non-target) is crucial as well, especially now when weed management is directed towards the integration of multiple approaches.

An important genetic factor to consider is the ploidy level of each weed population. Briefly, many of the most problematic grasses are polyploids, which are genetically more diverse [127]. Their gene redundancy should enable more mutation diversity in HR genes, and it may promote a faster evolution towards resistance. However, in these species, the resistance magnitude conferred by a mutation in one gene may be diluted by multiple sister alleles, resulting in a negative correlation between the copy-number of the target gene and the resistance level [128]. There are only few studies that have attempted to determine the potential link between ploidy and evolution of HR plants. For example, Yu et al. [129] reported that a hexaploid wild oat (*Avena fatua*) was resistant to ACCase inhibitors, and they found a negative association between ploidy and herbicide resistance evolution.

Understanding a weed's resistance mechanisms to a herbicide is important in several ways. For example, in the case of glyphosate, revealing such mechanisms has allowed scientists to better comprehend glyphosate's mode of action and to develop methods to faithfully measure the rapid spread of resistance among weeds [21,130]. In addition, it is crucial to know which TSR and/or NTSR mechanisms a weed population contains so that the appropriate herbicide resistance management strategies may be used. For example, control of a weedy population containing the W574 substitution in ALS protein may require the rotation of herbicides with different MOA, because this mutation confers resistance to a broad range of ALS-inhibiting herbicides. Meanwhile, another TSR mechanism such as the A122 T substitution in ALS protein may allow the use of different chemicals within ALS-inhibiting herbicides, given that this mutation only confers resistance to the imidazolinone family [16]. On the contrary, the presence of NTSR mechanisms is more complex to interpret in terms of management decisions. This is mainly due to their high complexity, poor molecular characterization, and slow detection.

Different NTSR mechanisms were reported to be responsible for several cases of multiple resistance; interestingly, all of them were specific for one herbicide [59,90,93]. However, the possibility of a unique NTSR mechanism to cause cross-resistance cannot be ruled-out. For example, the overexpression of an antioxidant enzyme could prevent the lethal oxidative stress triggered by different herbicides [131]. Similarly, an alteration in certain transmembrane transporters could simultaneously affect the translocation of several active ingredients; or a change in a cyt P450 activity could trigger the metabolism of various herbicides as recently proposed by Shergill *et al.* [132]. Thus, the identification of a potentially unique NTSR mechanism in a weed population could prevent the use of more than one herbicide. The detection of NTSR systems could be of more practical use in weed management programs if a better understanding of the underlying mechanisms is acquired.

4. Is global climate change an unnoticed factor in herbicide resistance evolution?

As a result of climate change, weed flora of some arable ecosystems has suffered considerable transformations during the last decades [133]. For instance, a number of thermophile, late-emerging and opportunistic weeds have become more abundant in many cropping systems [134]. Therefore, weeds with high phenotypic plasticity regarding extreme weather events may be more likely to survive.

Although herbicide resistance mechanisms can be associated to fitness costs, fitness benefits endowing some adaptive advantages in the absence of herbicide selection pressure are also possible. Particularly, the presence of a considerable number of HR weed populations in areas never treated with herbicides could be explained by the fitness benefits

of mutations that confer such resistance. For instance, the I1781 L mutation in *ACCase* gene not only confers TSR, but also it increases biomass production of *Setaria italica* [135], and delays seed germination in Alopecurus myosuroides [136]. This last effect potentially allows this species to escape from early-season weed control measures [136]. Thus, a HR biotype can present additional advantages under particular environmental conditions even in the absence of herbicides. Accordingly, Délye et al. [137] have shown that the aforementioned mutation in ACCase from *A.* myosuroides was present in weed populations prior to herbicide selection in higher frequencies than those observed for de novo mutation., The authors refer to it as an 'efficient' resistance gene, i.e., a gene conferring resistance without significant deleterious pleiotropic effects.

Under global climate change, plant invasion rates have increased [138] and geographical patterns of highly competitive weeds have changed [139,140]. Therefore, gene-environment interactions should be studied to assess the indirect contribution of climate change on the evolution of herbicide resistance. Moreover, environmental conditions can directly influence the expression of HR genes, as was demonstrated by Vila-Aiub et al. [141]. In fact, Matzrafi et al. [142] have reported that climate change reduces herbicide efficacy on weeds in a metabolism-based manner and, consequently, increases risk of NTSR evolution. In this context, Markus et al. [131] discusses the effect of epigenetic changes on HR plants as a new perspective to understand how environmental stress can affect resistance evolution.

Since NTSR is part of the weed's response to abiotic stresses [50], it is valid to hypothesize that plants displaying it could be more likely to survive under particular stress conditions, such as high temperatures or altered precipitation patterns derived from climate change. If, indeed, there is such unnoticed selection pressure, it seems to be even more difficult to overcome than an irresponsible weed management.

5. Perspectives on weed resistance management

Weed management systems based solely on herbicides are not sustainable in the long term. Instead, a weed management program that combines multiple methods is highly recommended. Two fundamental approaches could be used to mitigate (proactive strategies) or control (reactive strategies) herbicide resistance. The former aims to reduce herbicide selection pressure by diversifying controlling procedures for weed management, which should minimize the survival and reproduction of resistant individuals; while the latter aims to diminish the spread of resistance due to seed production, pollen dispersion, and propagule dissemination [143].

Although the Integrative Weed Management (IWM) concept originated more than a half-century ago [144], its adoption has been quite unsuccessful. Farmers have largely failed to implement more proactive strategies, arguing greater costs and management complexity. Thus, the current management response to herbicide resistance is usually reactive, and multiple factors have been associated with this approach [143,145]. The main reasons for growers' lower adoption of proactive strategies are many: the increase in weed-control costs, the perception that the benefits of delaying resistance are uncertain, and the expectation that new herbicides will become available in the future [146,147]. Therefore, an improved understanding of the human component in weed management is required to approach this multidimensional topic [4,148,149].

Next, we propose several different practices that could be incorporated into an IWM program (IWMP) to approach a 'sustainable intensification' [150]. We discuss their potential use and the advantages and disadvantages each may have. Some of these practices are novel and have not been adopted yet. We have classified these strategies into two groups: 'proactive' and 'reactive' (see Fig. 2). Although this categorization is not strict (no strategy belongs exclusively to a unique group), it helps to highlight the predominant usefulness of each one.

5.1. Traditional agronomic practices and technologies

5.1.1. Crop rotation

One of the most promising strategies in weed management is the design of a crop rotation system based on sound agronomic knowledge, since weed population density and biomass production can be significantly reduced using a temporal diversification scheme [151]. Moreover, a key benefit of rotational diversity is that it facilitates herbicide diversity due to the different MOAs available for different crops.

Crop rotation may create environments that limit the growth and proliferation of particular weed species due to the greatest variability regarding soil disruption, competition for resources, allelopathic effects, and mechanical damage [152]. Thus, this practice helps to diversify weed management programs, decreasing the selection pressure that favours the dominance of a few weedy species in a given field [153].

Green manures and cover crops (soil-improving or soil conservation crops) may also become part of a rotation system, and they are planted in seasons when main crops are not cultivated. However, these practices are mainly used in special situations, such as organic farming [154]. Cover crops not only reduce weed proliferation during fallow but also increase microbial activity in soil [155], which could favour herbicide degradation. Rye (*Secale cereale*), barley (*Hordeum vulgare*), wheat (*Triticum spp*), and oat (*Avena sativa*) seem to be the most weed-suppressive gramineous cover crops. Thus, for example, cereal rye cover crops (*Secale cereale L.*) not only reduced Palmer amaranth biomass in cotton fields but also retarded the critical period for weed control [156]. On the other hand, legume cover crops offer another alternative for weed management, with the supplementary advantage of reducing the use of synthetic nitrogen fertilizer.

It is important to point out that herbicides are typically used for cover crop termination before main crop planting [157]. Although these herbicides are usually non-selective and with low carryover, recent research has focused on improving mechanical termination with rollers or crimpers, which may contribute to diversifying practices and to avoiding vicious application cycles [158].

Even though many aspects of crop rotations are compatible with current farming practices, they have not been widely adopted by farmers compared to other recommended management strategies. The reasons are multifaceted, and they include socioeconomic as well as biological factors, which have been discussed in detail by Hurley and Frisvold [145]. Herein we would like to highlight that, in the short run, crop rotation systems may cause lower economic returns than monoculture systems. This economic factor, together with simpler equipment, knowledge and practical experience required by monoculture systems, explains why crop rotations have been dramatically simplified in the last decades [154].

5.1.2. Herbicide rotation and mixtures

The undesirable ecological shift in weed flora due to the use of a single herbicide, along with the fact that weeds can become resistant to any herbicide that is not properly used, are two lessons learned from glyphosate overuse. Nowadays, herbicide rotations, herbicide combinations and, even more, rotation of herbicide mixtures are the most recommended chemical practices. All these strategies rely on the assumption that newly emerged HR alleles will decrease in frequency upon the removal of the selection pressure favouring such alleles [159].

In herbicide rotation, two or more herbicides are selected for weed control, and then the practice is to rotate between the different herbicides every season. In this way, the selection pressure carried out by each herbicide is minimized. In the absence of each herbicide, a lower resistance evolution rate could derive from a significant fitness cost associated to a particular mechanism causing resistance to that herbicide. However, this strategy could not be effective if the fitness cost is limited, as it was demonstrated by Wu et al. [160].

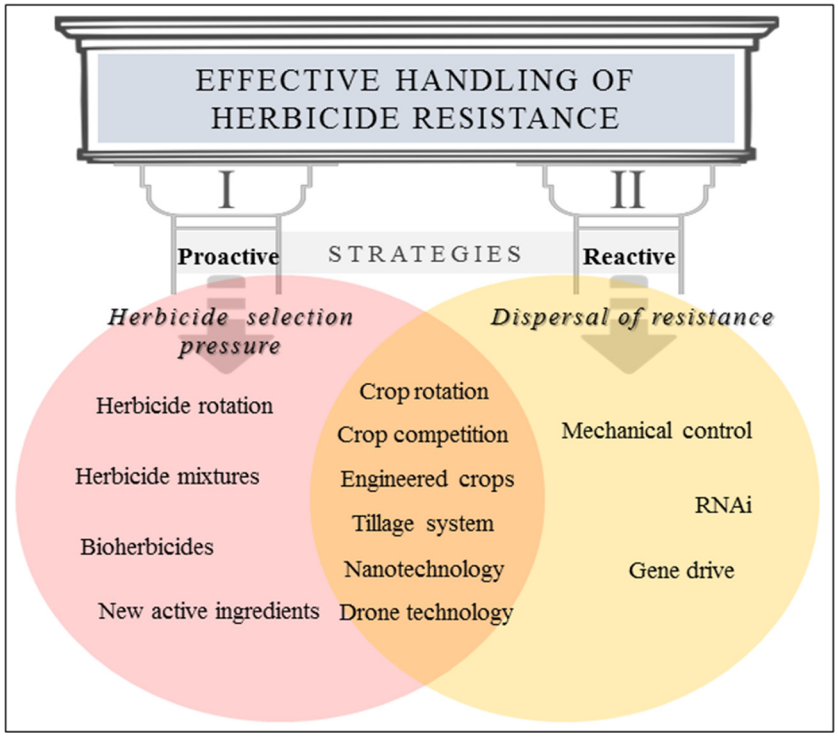

Fig. 2. Classification of strategies for an effective handling of herbicide resistance.
Strategies for an effective handling of herbicide resistance can be classified into proactive (to mitigate resistance evolution) and reactive (to reestablish control after resistance emerged). See sections 5.1 and 5.2 for a complete description of each strategy.

Interestingly, when herbicide mixtures were used a delayed selection of HR weeds was observed in comparison to the sequential application of herbicides with different MOAs [161,162]. However, in an attempt to reduce costs, herbicide mixtures are often applied at doses below the recommended rates [151]. The use of sublethal doses should be avoided because it increases the risk of selecting NTSR mechanisms or cross-resistance [163–165]. Moreover, herbicide selection for mixing requires special care, since some herbicides have shown antagonistic effects when combined [166,167].

5.1.3. Tillage system

Tillage systems have a notorious impact on weed species seedbank composition, seed abundance and seed depth-distribution in the soil [168]. In no-tillage (NT) systems, seeds tend to accumulate near the soil surface, while moldboard plowing followed by disking buries them. Consequently, in NT systems the dominant weed species should be those whose seeds are adapted to survive, germinate and grow near the soil surface. In contrast, species whose germination requires burial-induced dormancy break or predator protection will be dominant in tillage systems. Thus, perennial weed abundance increases after several years of reduced tillage, given that the disturbance of vegetative propagules is lower and seeds remain near the surface [5]. Purple and yellow nutsedge (*Cyperus* sp. L) and johnsongrass (Shorghum halepense L.) expansion is a clear consequence of this phenomenon, which contributes to the ability of these species to develop herbicide resistance [169,170]. Therefore, one way to control these problematic weeds could be the occasional use of tillage practices in a NT system, since they are the best means to disturb vegetative propagules and restore the balance in soil seedbanks [151]. Thus, this mechanical weed control has been re-adopted by growers in the last few years, but it still represents an agronomic setback compared to the advantages of NT systems (e.g. reduced erosion, improved soil structure, and increased soil water holding capacity, soil organic matter, carbon sequestration in soil, and soil biodiversity).

5.1.4. Crop competition

This tactic aims to maximize the ability of the crop to compete for water, light, space, and nutrients, and to avoid problems related with the intensive use of herbicides.

Selecting appropriate cultivars and planting patterns may reduce weed-induced yield loss by increasing the crops' ability to outcompete weeds for resources. One of the first studies demonstrating the effectiveness of this weed management strategy was carried out using three weed-suppressive Asian rice cultivars, in comparison to four US cultivars [171]. Later, effective weed control was achieved in wheat, sorghum, canola, maize and soybean by selecting appropriate row spacing, row orientation, planting frequency, plant density and cultivars with high competitive aptitudes (e.g. high biomass, quick growth, rapid germination, large leaf area, and production of allelochemicals) [172–177].

Crop competition strategies not only reduce yield loss, but they may also decrease selection pressure and herbicide dependence for weed control. Thus, they could diminish the negative impact that herbicide overuse has on the environment.

Despite the potential that crop competition strategies have as environment-friendly weed management tools, they are underexploited [178]. Poor understanding of weed-crop interactions hinders the development of sustainable and cost-effective crop competition tactics [179,180]. Nevertheless, they should become an essential component of IWMP as both proactive and reactive responses against herbicide resistance selection.

5.1.5. Genetically engineered crops

Maintaining or increasing herbicide diversity certainly plays an important role in the management of HR weeds. Genetically engineered (GE) crops have been blamed for increased problems with HR weeds since they may cause significant changes in herbicide use patterns. A recent analysis to quantify the impact of GE crops on the herbicide resistance evolution rate in the US demonstrated that the adoption of HR varieties substantially reduced herbicide diversity in cotton and soybean, increasing selection pressure for HR weeds in both crops, while adopting GE corn varieties did not reduce herbicide diversity [181].

Stacking HR genes into a single crop offers the possibility to rotate and/or combine different herbicides to delay herbicide resistance evolution in weeds. New engineered major crops with resistance to 2,4-D,

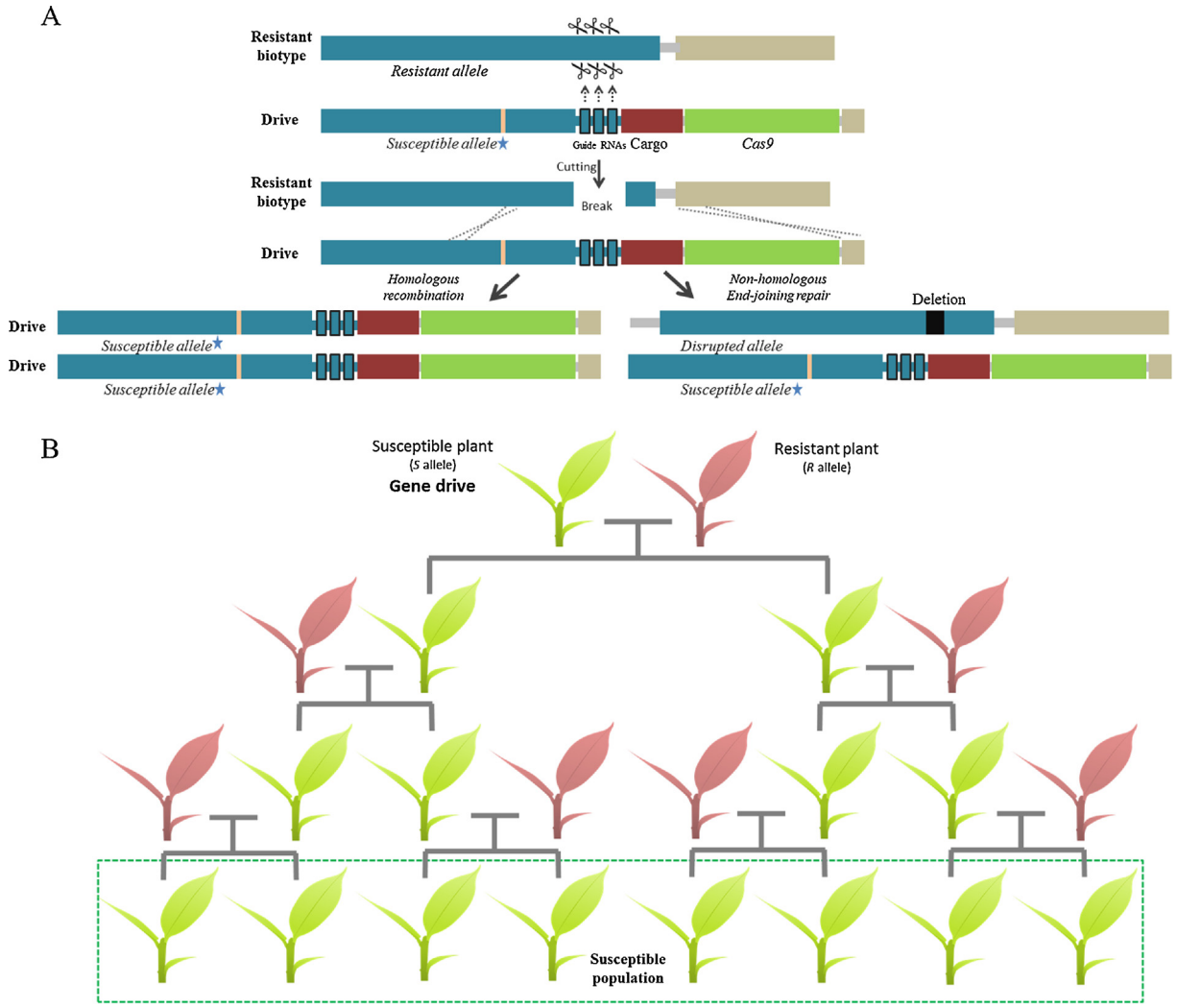

Fig. 3. Reversion of resistant trait through gene drive technology.
A. A drive gene carrying a susceptible allele of a HR-target gene within a Cas9-sgRNA construct is used to replace the sister resistant allele present in the homologous chromosome. Directed by a few sgRNA, Cas9 endonuclease reliably cuts target sequences and makes a break that allow the cell repairing systems to work through homologous recombination or non-homologous end-joining repair. B. When a susceptible plant carrying an endonuclease gene drive (green) mates with a HR plant (red), the gene drive is preferentially inherited by all offspring. This can enable the drive to spread until it is present in all members of the population. Adapted from Esvelt et al. [210].

dicamba and inhibitors of HPPD, ACCase or ALS, either alone or combined with glyphosate and/or glufosinate resistance, are on the way [182]. However, strategies exclusively based on chemical control will not be reliable in the long term because evolution will override herbicide efficacy, as it has been demonstrated by the increasing number of multiple resistance cases [34]. Therefore, these new tools should be used more responsibly than in the past to extend their benefits and to minimize undesired effects.

On the other hand, a rational design of new HR alleles by directed evolution studies, associated with new breeding techniques, such as directed mutagenesis by oligonucleotide –ODMs– or genetically engineered –ZF, TALE or CRISPR– nucleases, are in the pipeline as novel contributions to the HR weed problem. These novel technologies were already applied to herbicide resistance in crops: a canola resistant to ALS inhibitors (SU Canola™) was obtained by precision gene editing, mediated by ODMs. This innovative development was carried out by Cybus, *the Rapid Trait Development System (RTDS)* [183], which is now available in the United States. Although these technologies would allow for the development of products with similar resistances to those already available, in many countries the legal regulation processes for these GMOs are generally faster than those for transgenic crops [184]. Thus, the release of edited resistant crops would be easier and would increase the variety of tools available for rotation.

5.2. Modern and promising technologies

5.2.1. Bioherbicides

The development of new herbicides is of great importance because the effectiveness of commercially available ones is decreasing dramatically, and chemical weed control still remains the most widespread agronomic practice. 'Allelochemicals' are natural substances that could be used as bioherbicides. These compounds participate in allelopathy, a natural phenomenon that involves the interactions among plant species and microorganisms through the synthesis of a wide variety of biocommunicators. Allelochemicals are secondary metabolites exuded by plants, and they can affect the germination and growth of neighboring plants by interfering with different physiological processes such as photosynthesis, respiration, and water or hormonal balance [180]. These natural products provide an attractive alternative to find competent and environment-friendly herbicidal compounds with high structural diversity and novel MOAs.

Several allelochemicals have been described in various plants

Table 2
Pros and cons of strategies and technologies for herbicide resistance mitigation.

Strategy / Technology	Pros	Cons
Crop rotation Cover crops Green manures	- Promotion of herbicide diversification (rotation of herbicide MOAs). - Reduction of herbicide applications. - Improvement of biological, chemical and physical soil properties. - Low environmental impact.	- More labor-intensive than monoculture systems. - Lower economic returns in the short term than monoculture systems. - Termination trouble for cover crops.
Herbicide rotation and mixtures	- Delay in the evolution of new HR weeds (better for mixture of MOAs than for sequential use of MOAs). - Mixture of MOAs allows the use of lower doses, meaning lower cost.	- Mixture of herbicides requires the consideration of eventual antagonistic events. - Herbicide sub-doses may induce the evolution of NTSR mechanisms.
Tillage system	- Control of vegetative propagules. - Restoration of balance in soil seedbanks by alternated use of tillage practices in a no-tillage system.	- - Loss of the no-tillage system benefits (less soil erosion, conservation of soil structure and moisture, minimum fuel and labor costs, etc.).
Crop competition	- Optimization of natural resources utilization. - Reduction of herbicide applications. - Low environmental impact.	- Little development of competitive cultivars for some crops.
Genetically engineered HR crops	- Fast and easy adoption. - Diversification in herbicide use (by the stacking of different HR genes in a crop).	- Herbicide-dependence. - Acceleration in the selection of weeds with multiple resistance.
Bioherbicides	- High structural diversity and novel MOAs. - Less surfactant usage because of high water solubility. - Low environmental impact.	- Low specificity and low selectivity. - Highly dose-dependence. - Possible phytotoxic effects. - Short half-life.
Innovative mechanical weed control	- Rapid effect. - Reduction of the weed seedbank.	- Expensive equipment. - Difficulty in the adaptation to control different weed species.
Precision and smart agriculture	- Minimum herbicide dose usage. - High precision of herbicide spraying with highly sensitive sensors and high quality image software. - Nanoscale formulation can improve the effectiveness of allelopathins.	- High development costs. - Low economic feasibility. - Low autonomy of drones for high extension fields.
RNAi Gene drive	- Prevention of the spread of HR weeds by restoring herbicide susceptibility. - Possibility of re-starting a weed management program using all the available tools.	- Not easily applicable to weeds with polygenic NTSR mechanisms. - High development costs. - RNAi can only be used during fallow or prior to crop emergence, in combination with the herbicide. - RNAi molecule is highly unstable and susceptible to degradation. Formulation has to guarantee its stability. - Gene drive requires up to 20 generations to totally restore herbicide susceptibility in the population, and its success is highly dependent on the cooperation among neighbor fields. - Gene drive is not easily applicable for all weed species. Outcrossing and diploid species are most suitable. - Pollen delivery issues associated to gene drive technology. - Little development of the ethical and legal framework for gene drive usage regulation.

[185–188]. Sorgoleone is one of the most characterized allelopathic chemicals. It is released from the root exudates of *Sorghum bicolor* and is predominantly concentrated in the living root hairs. This molecule inhibits weed growth without affecting the cultivated crop species, making sorghum a good option for crop rotation [189].

Although some plant extracts can be successfully used for weed control, and thus be incorporated in IWMP, reduced profitability hinders their in-field application. Hence, research has focused on the isolation of single compounds which may be formulated and directly used as bioherbicides or used as lead structures for the development of new products by chemical modifications. Nonetheless, a common problem with bioassay-guided isolation of bioactive compounds is that the activity of a mixture cannot always be explained in terms of the activity of one or more of the components, since there may be additive or synergistic effects [190].

Most allelopathins are totally or partially water-soluble, which makes them easier to apply without the need of additional surfactants [191]. Moreover, their chemical structures are more environment-friendly than synthetic ones, since their half-life is shorter. Nevertheless, this eco-friendly property may shorten the period of activity. Regarding this, the chemical industry has developed several synthetic modifications to obtain analogous active ingredients with higher stability, such as mesotrione [192] and sarmentine [193].

In summary, allelochemicals are very attractive as new classes of herbicides due to various advantages. Besides the benefits of using natural compounds in crop protection, they would also represent a possibility to cope with herbicide resistance evolution in weeds, since the probability of resistance appearance is lower as multiple targets are affected [194,195]. Nonetheless, this multi-site action in plants makes the bioherbicide effects non-specific, non-selective, highly dose-dependent and, in some cases, phytotoxic. Consequently, the use of an allelopathin as a potential bioherbicide is possible, but rather restricted to a particular crop with a defined weed composition [196]. This intrinsic non-selectivity and short half-life lead to erratic performance in field conditions, largely explaining why there is no bioherbicide under extensive adoption yet [197].

5.2.2. Innovative mechanical weed control

In farms where HR weed density has increased beyond a certain point and available control strategies have been proved ineffective, mechanical weed control remains the only means to restore productivity. Current research is directed to the development of machine vision technologies for weed control practices that allow the operation and control of mechanical devices with neither human intervention nor coverage destruction. For instance, a weed-detecting robotic model for sugarcane fields has been recently developed [198]. This robotic prototype faithfully identifies the sugarcane crop among nine different weed species. However, the mechanical weed control system consisting

of a rotavator blade and a robotic arm that uproots or removes weeds has not been completely built yet. Many other technologies for physical weed control (e.g. hot water, soil steaming, flaming, electrocution) are being developed and tested upon different conditions. For a detailed description of the state-of-the-art of each one, we recommend Korres et al.'s recently published work [199].

At present, there is a new tool that allows weed seed control. This is the integrated Harrington Seed Destructor (iHSD)®, which intercepts and destroys weed seeds during harvest [200] and, thus, it reduces the weed seedbank for the next season. The iHSD was found to destroy 99% of Palmer amaranth seeds in soybean fields [201]. Up to now, this novel weed control practice has not been extensively adopted yet, probably because of the need that exists to adapt this technology to different weed species. However, it is likely that iHSD will be soon adopted in fields with high densities of Palmer amaranth to reduce the contribution of this dominant species to the soil seedbank.

5.2.3. Precision and smart agriculture

Precision and smart agriculture can improve management efficiency of agricultural inputs and reduce the environmental impact of crop production systems by using site-specific information [202]. Nowadays, different image processing techniques can be used for real-time weed identification [203]. Real-time localized spraying includes sensor-based plant identification and instant herbicide application over the target weed. This may minimize the total quantity of herbicide applied and consequently reduce the HR weed evolution rate. In the near future, robotic and drone technologies could improve on-time field scouting by using electronic hardware, software and sensors that may allow to distinguish among crops and weeds. In this sense, Utstumo et al. [204] have recently presented a robot equipped with a GPS and a drop-on-demand system that identifies weeds in a field row and sprays extremely low doses (micrograms) of herbicide over them. Nevertheless, these tools are limited for current agricultural production because there are still many challenges in weed control in large fields [151], particularly because of low drone autonomy.

Agro-nanotechnology may also contribute to weed management. If herbicide release is controlled by nanoencapsulation of the active ingredient, then repeated in-field applications of herbicides will be minimized, and the adverse effects on plants and the environment might be reduced as well [205,206]. Recently, Zhao et al. [207] highlighted the importance of nanoscale eco-friendly formulation of pesticides, like allelopathins, which may meet the requirements of biocompatibility and bioavailability, allowing the insertion of different strategies into IWMP and contributing to developing and implementing green nanotechnology [208]. However, more research and further development are needed before these tools can be commercialized.

5.2.4. RNAi and gene drive technologies: restoring the herbicide susceptibility

In the 'omic and bioinformatic' era, the use of new technologies for weed management is promising. It has been suggested that RNA interference (RNAi) technology (branded BioDirect™ by Monsanto) could help to control HR weeds by restoring their herbicide susceptibility just before herbicide application [209].In the best known example of this, a mixture of glyphosate and double-stranded RNA coded to bind the *EPSPS* gene is sprayed over weeds during fallow, triggering efficient local and systemic silencing of the HR gene and allowing the glyphosate to kill the plants. This technique also involves the spraying of a silicone surfactant on the plant's surface that lets the RNA molecules slip through the stomata (Patent WO 2011112570 A1).

Recently, Dalakouras et al. [210] have stated that the induction of silencing in plants by high-pressure spraying of *in vitro*-synthesized small RNAs is faster and more effective when targeting the apical meristem than spraying mature leaves. The stability of dsRNA in the agronomic formulation is a point of major concern because the molecule must join the RISC complex (RNA-induced silencing complex) in the plant and induce the silencing machinery. Furthermore, this approach is not suitable for polygenic NTSR, and it is still in the early stages of development.

Another promising tool is gene drive technology, which could be used to restore herbicide susceptibility in HR weeds. The gene drive process can be conducted by the introduction of a cassette containing the coding sequences for the Cas9 endonuclease and a single-guide RNA (sgRNA) into a specific target gene of an organism [211]. Next, the cassette is automatically copied into the sister allele of the homologous chromosome. The employment of this technique could have many applications since it could figure the genome edition of entire populations.

If the pollen of a plant that carries the cassette of interest (with a herbicide-sensitive gene and Cas9 gene) fertilizes the egg cell of a HR weed individual, the target gene of the haploid egg cell will be quickly converted into its modified version (Fig. 3A). As the enzyme is guided to cut the wild-type homologous chromosome at the target site, and the cell repairs the cut via homologous recombination using the drive gene chromosome as a template, the endonuclease drive genes are preferentially inherited. If the endonuclease does not cut, or the cut is repaired via non-homologous end-joining repair, the drive is not copied. Although these alternative mechanisms generally occur in low frequency and are not an impediment to the dissemination of the gene within the population, their incidence may vary among species and even among tissues [211].

Thus, the introduction of a Cas9/sgRNA construct into a HR weed could replace the resistant allele by its susceptible version. Rapid spread of this gene, due to the super-Mendelian inheritance driven by this technology, could greatly suppress proliferation and further dissemination of the HR weed biotypes (Fig. 3B) [211,212]. Gene drive has already been tested in yeast, mosquito and *Drosophila* systems, and it was found that the frequency of the modified gene increases with successive generations [213–215]. Some modeling studies estimated that it would take up to 20 generations for the edited gene to be fixed in a plant population [216]. Thus, this technology would be harshly limited in selfing and in perennial weed species and unachievable in those with vegetative reproduction.

Despite some technical and many ethical limitations, it is important to define on which weed species gene drive technology would be more feasible. According to Neve [217], the most suitable target species would be *Amaranthus palmeri*, *Amaranthus tuberculatus*, *Alopecurus mysuroides* and *Lolium rigidum*, all outcrossing, diploid species with a very high resistance risk.

Paradoxically, a resistance to the gene drive has been reported, and is a main issue of this new technology [218]. This resistance can be generated by two mechanisms: natural genetic variations present in the target recognition sequence within the population, or errors –insertions/deletions– introduced by the system when repairing the cut, which makes the sequence no longer recognizable. Thus, some researchers suggested that this technology could result in the development of genetically isolated populations that may avoid the inheritance of the modified code [219]. Moreover, it is still unpredictable how gene drive would behave in wild populations, mainly because it could spread indefinitely and eventually disturb the agroecosystems. In this way, scientists are testing new approaches called 'daisy drive' and 'split-drive' in their ability to affect only local environments, controlling the number of generations during which the system is active by placing the edited gene under the control of a second gene with Mendelian inheritance [220,221].

Although current research is focusing on the possibility of simultaneously editing multiple target sequences to slow the evolution of HR weeds [222], most scientists emphasize the need to plan and think carefully about potential risks before gene drive technology is released to the wild environment.

Furthermore, neighbor effects can influence the success of almost all weed management strategies [223]. These effects particularly condition gene drive´s effectiveness, since the careful coordination between

neighboring fields is essential to guarantee that herbicide susceptibility is accurately restored. In this context, the role of the government, companies and scientists is central to achieve coordinated decisions.

Table 2 summarizes the positive and negative points discussed for each strategy.

6. Concluding remarks

In this review article, we discussed the current global status of HR weeds. We indicated global climate change as an unnoticed factor that may be acting on their selection, especially those evolving into NTSR mechanisms. We also discussed the pros and cons of a number of tools that could be adopted to cope with herbicide resistance evolution in weeds. Although some of them (e.g., gene drive and RNAi technologies) exhibit a strong potential to mitigate this undesirable selection, concerns about possible ecological disturbances still prevent their application at the field level. Therefore, we highlighted the importance to incorporate several underexploited conventional strategies into IWMP. The rational use of herbicide mixtures, crop rotations, cover crops, crops with higher competitiveness against weeds and the use of precision agriculture tools (including eco-nanotechnology) are highly recommended and applicable agronomic practices. Moreover, the identification of which mechanism (TSR and/or NTSR) is present in a certain weed population is very useful for weed management decisions. Nevertheless, a question remains: how extensive or rapid will the adoption of these integrative strategies by farmers around the world be? Finding the answer to this question will be one of the most important challenges in agriculture for the coming years.

CRediT authorship contribution statement

Valeria E. Perotti: Conceptualization, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Alvaro S. Larran:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Valeria E. Palmieri:** Writing - original draft. **Andrea K. Martinatto:** Writing - original draft. **Hugo R. Permingeat:** Investigation, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare no conflict of interest.

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