Chapter 5

Biochemical and Molecular Knowledge about Developing Herbicide-Resistant Weeds

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Abstract

Herbicide resistance is the genetic capacity of a weed population to survive an herbicide treatment that, under normal use conditions, would effectively control the resistant weed population. Weeds have been evolving in conventional crop cultivars worldwide from selection pressure placed on them from repeated use of herbicides. In this chapter, we intend to explain the biochemical and molecular basis of herbicide resistance in weeds. On the other hand, herbicide resistance can be a useful tool so that weed scientists can use as important approach to control and manage weeds. There are several strategies for the production of HR crops by genetic engineering and the methods used in this process will be discussed in this chapter.

Keywords: herbicide resistance, biochemical mechanisms, molecular basis

1. Introduction

Humans have travelled a long way reaching the agriculutre that is there today. In the initial days, weed control has been a major concern in crop production and different approaches have been tested to manage weeds. Some approaches have been retired after several years and others still being adopted. Herbicide application is one of the approaches that still remain durable and efficient. Similarly, for every Human-made strategy, herbicide application has both positive and negative effects. Herbicides have increased agricultural productivity effectively, but on the other hand, has caused a serious problem by promoting the evolution of herbicide-resistant weeds. Successive applications of some herbicides of the same group or some herbicides with the same mode of action in a field will contribute resistance to herbicides in

one or several weed species. In spite of some concerns about weed resistance to herbicides, only a logical approach integrates all common strategies to inhabit herbicide resistance in weeds because the Human population is ever increasing.

Although development of resistance in weeds is an undesirable phenomenon, herbicide tolerance in crops is favorable. If the principle crop is not always tolerant to the herbicide, the herbicide will either decrease the productiveness of the primary crop or kill it. If the herbicide is not strong enough, it could allow the proliferation of weeds within the crop field thus affecting the productiveness of the primary crop. It is therefore desirable to produce crops that are tolerant to herbicides. The important objectives of this chapter are to clearly explain the important biochemical and molecular reasons of herbicide resistance in weeds, and and at the same time investigate the methods for the production of HR crops.

2. Definitions of tolerance and resistance

Generally, herbicide has very beneficial effects on agricultural production worldwide [1]. Herbicides are often the most reliable and economical option available to control weeds [2, 3]. The availability of herbicide has allowed that researchers modify plant height and transform plants for increased performance [4]. Efficiency and cost-effectiveness of herbicides has led to positive impact on the agricultural production systems in the developed countries [5]. Herbicide tolerance and herbicide resistance are two very important concepts that should be carefully considered. Standard definitions of the herbicide "tolerance" and "resistance" based on the crop and weed biology were established by the Weed Science Society of America (WSSA) in 1998. According to the definitions of the WSSA, tolerance is the inborn capacity of plant groups to survive and recreate after herbicide treatment. This infers there was no election or genetic manipulation to make the plant tolerant; it is naturally tolerant. Resistance is "the acquired capacity of a plant to survive and propagate after introduction to a dosage of herbicide typically deadly to the wild sort. Resistance may be innately happening or initiated by such strategies as genetic engineering or election of variations created by tissue culture or mutagenesis [6].

3. Herbicide resistance mechanisms

Fundamentally, two types of mechanisms are involved in resistance. Target-site resistance (TSR) is caused by changes in the tridimensional structure of the herbicide target protein that decreases herbicide binding, or by increased activity of the target protein. TSR is conferred by gene mutations in target enzymes such as 5-enolpyruvylshikimate-3-phosphate synthase, which is reported in many resistant weed species [7–9]. Non-target-site resistance (NTSR) is endowed by any mechanism not belonging to TSR, e.g., reduction in herbicide uptake or translocation in the plant, or enhanced herbicide detoxification [8, 10]. Mutations endowing herbicide resistance can be classified into two types. The first type is structural changes in a

DNA sequence encoding a protein, i.e., structural mutations. Structural mutations endowing herbicide resistance are expected to cause a structural modification in the tridimensional structure of a protein that will lead to a decrease in the efficacy of an herbicide. For example, mutations conferring an amino acid substitution at the herbicide-binding site of a target protein can decrease the affinity of the herbicide for the target protein (TSR). Alternatively, mutations at the active site of a metabolic enzyme or a transporter protein can improve the activity of these proteins in herbicide degradation or compartmentation away from its site of action, respectively (NTSR). In the case of structural changes in DNA sequence, seeking the cause for resistance means identifying and being able to detect the relevant structural mutations in the DNA of resistant plants. The second type of mutations associated with herbicide resistance results in a difference in the expression of one or several genes in resistant plants compared to sensitive plants, i.e., regulatory mutations [11, 12]. These mutations are changes in a DNA sequence that can cause an increase in the expression of the herbicide target protein that compensates for the herbicide inhibitory action (TSR), or a variation in the expression of herbicide-metabolizing enzyme(s) or of transporter proteins that will lead to an increase in herbicide degradation or compartmentation away from its site of action, respectively (NTSR) [13]. Non-target-site resistance compared with target-site resistance is less investigated especially in broadleaf weed species. Non-target-site resistance may cause weeds evolve unforeseeable resistance to diverse herbicides of different modes of action [14].

3.1. Target-site resistance

3.1.1. Resistance to protoporphyrinogen IX oxidase-inhibiting herbicides

Protoporphyrinogen oxidase (Protox), the target site of the diphenylether herbicides, catalyzes the conversion of protoporphyrinogen to protoporphyrin IX in tetrapyrrole biosynthesis. Several herbicides including the diphenylethers and oxidiazoles inhibit PPO. Inhibition of Protox leads to the production of large quantities of free protoporphyrin IX in the cytoplasm, which causes photodynamic damage in the presence of light and oxygen [15]. Results of investigations with a resistant *Amaranthus tuberculatus* biotype have showed an unprecedented and unanticipated mutation in which resistance is endowed by an amino acid deletion. Presumably, chloroplastic and mitochondrial protoporphyrinogen oxidase encodes by the PPX2L gene in resistant *Amaranthus tuberculatus*, there is the lack of a 3-bp codon, bringing an elimination of glycine at position 210 [16]. It is the just reportage card of codon/amino acid omission presenting resistance to herbicide. The Gly-210 elimination in the protoporphyrinogen oxidase gene confers extremely rate resistance to protoporphyrinogen oxidase herbicides by minimal impact on the natural inclination of protoporphyrinogen oxidase for its substrate protogen; however, the omission causes 10-fold lower protoporphyrinogen oxidase activity toward the ferocious sort [17]. However, resistance to Protox inhibitors has been selected for cell cultures [18] and has been generated in transgenic plants expressing heterologous Protox genes [15]. For example, a Protox Val389 to meet substitution endowed resistance in a selected *Chlamydomonas reinhardtii* line [19]. It has been proposed that the introduced resistant forms of Protox would need to replace rather than simply supplying the endogenous plant enzyme in order to avoid production of the toxic oxygen species following herbicide treatment [15, 20].

An obvious question is whether Gly-210 substitution, rather than deletion, would endow resistance. Modeling demonstrated that substitutions at Gly-210 provide either little or no resistance, or greatly decrease PPO functionality [56]. The necessity for contemporary absence of three nucleotides in the encoding succession of the focus gene, in addition to the duplex focusing of the gene result should chloroplasts and mitochondria, ought to restrict the development about this omission resistance mechanism, however it has been demonstrated in a further four resistant *A. tuberculatus* societies [21].

3.1.2. Resistance to tubulin assembly inhibiting herbicides

Both target-site resistance and non-target-site resistance to tubulin herbicides exist [22]. Target-site-based resistance to dinitroaniline herbicides has evolved in several species, such as *Setaria viridis* and *Eleusine indica*. Dinitroaniline and other tubulin-inhibiting herbicides have been used for several decades, and evolved resistance has been reported in some weed species (only 12 weed species) [23]. The mode of action of this group of herbicides is to bind to plant tubulin dimers and disrupting microtubule growth [24, 25]. In fact, these herbicides inhibit cell division by binding to the tubulin monomers, preventing their polymerization and spindle fiber formation [24]. Microtubules are polymers of α- and β-tubulin dimers and are involved in many essential cellular processes, including mitosis, cytokinesis, and vesicular transport [23]. Several possible resistance mechanisms have been proposed, including microtubule hyperstabilization and posttranslational modification [26, 27], but decisive document for these is still wanting. However, witness is beginning to stack up for target-site mutations. Analysis of resistant *Eleusine indica* biotypes has shown that a Thr239 to Ile mutation in a a-tubulin gene endows a high level of resistance, provided a Met268 to Thr mutation confers a lower or intermediate level of resistance [28, 29]. The Thr239 to Ile mutation conferred resistance to oryzalin, pendimethalin, and amiprophos-methyl, but not to pronamide in transgenic tobacco [30]. Similarly, Lys350 to Glu or Met mutations in a b-tubulin gene conferred resistance to colchicine (which also inhibits cell division) in *Chlamydomonas reinhardtii* [31]. However, the latter mutations have not been reported in any higher plant resistant to dinitroaniline herbicides [15].

3.1.3. Resistance to 5-enolpyruvylshikimate-3-phosphate synthase inhibitors

Glyphosate, a widely used nonselective herbicide, inhibits 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), a key enzyme in the biosynthesis of the aromatic amino acids phenylalanine and tyrosine [15]. Glyphosate inhibits potently the chloroplast enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which catalyzes the reaction of shikimate-3-phosphate (S3P) and phosphoenolpyruvate (PEP) to form 5-enolpyruvylshikimate-3-phosphate (EPSP). Glyphosate blockage of EPSPS activity interrupts the shikimate pathway and prevents aromatic amino acid product, ultimately causing plant death [32].

A major factor accelerating the evolution of glyphosate-resistant weeds has been the advent of transgenic glyphosate-resistant crops, such as soybean, maize, cotton, and canola. In these crops, glyphosate has replaced almost all other herbicides or other means of achieving weed control. From an evolutionary viewpoint, this singular reliance on glyphosate is an intense

selection for any glyphosate-resistance genes [33, 9]. A serine substitution at Pro-106 (Pro-106-Ser) in an extremely conserved district of the EPSPS gene creates target-site glyphosate resistance, which was first observed in an *Eleusine indica* biotype [34, 35]. After that, as a first report, in glyphosate-resistant *E. indica* and *Lolium* populations have been first detected threonine and alanine substitutions at Pro-106 [36, 37]. Pro-106 (Pro-106-Ser) amino acid substitutions have been recognized in *E. indica* and also *Lolium* populations around the globe. These Pro-106 substitutions confer only a modest degree of glyphosate resistance [38].

Some researchers suggest that the resistant population of *Lolium rigidum* presents three different mechanisms of resistance to glyphosate, namely reduced absorption, reduced mobility in the plants, and a mutation in the gene coding for the enzyme targeted by glyphosate [39]. The crystal structure of *Escherichia coli* EPSPS and molecular modeling displays that glyphosate barricades EPSPS by engrossing the PEP binding site [40, 41]. Based on results of a decisive study on *E. coli* EPSPS Pro-106 substitutions and the crystal structure of EPSPS-S3P-glyphosate, it was found that a little restricted of the glyphosate/PEP binding site hole is created by Pro-106 substitutions, which maintains EPSPS functionality but confers glyphosate resistance [40]. In comparison, high-level glyphosate resistance is conferred by substitutions at Gly-101 or Thr-102, which decreases the content of the glyphosate/PEP binding and also this significantly decreases dependence for PEP [42]. Therefore, the protecting of EPSPS functionality may be very scarce in mutations, empowering both glyphosate and PEP binding [43].

It was shown that more than 40-fold EPSPS overexpress as a result of up to 100-fold EPSPS gene amplification. There are some evidences that proofed this fact in highly glyphosate-resistant *Amaranthus palmeri* biotypes several years ago. This inheritable EPSPS gene amplification can affect the expression level and glyphosate resistance segregating in F2 generation plants [44]. Nowadays, some laboratory attempts is doing to protect this kind of field-evolved resistance by selection of glyphosate-resistant cell lines from several plant species with EPSPS gene amplification. For example, it was shown a three-fold increase in basal EPSPS mRNA and enzyme activity in glyphosate-resistant *L. rigidum*, and a supplementary higher EPSPS expression in some glyphosate-resistant *Conyza* biotypes. However, in these given species, glyphosate translocation decrease considers as the most important resistance mechanism [45, 46]. Breeders showed although EPSPS relative copy number in nuclear genome can positively influence EPSPS mRNA level, EPSPS protein amount and activity female parents have major role than male parents in transformation of resistance inheritance [47].

Multiple herbicide resistance evolves various heterologous resistance mechanisms enciphered by particular resistance genes that coexist at the individual and/or population level, conferring resistance to several herbicides with different modes of action. Given its significance in modern agriculture, the most serious multiple herbicide resistance scenarios are those involving glyphosate [48].

3.1.4. Resistance to ACCase-inhibiting herbicides

The aryloxyphenoxypropionate (AOPP) and cyclohexanedione (CHD) herbicides inhibit acetyl-CoA carboxylase (ACCase) [49, 50]. Two types of ACCase have been identified: the heteromeric prokaryotic ACCase is composed of multiple subunits, whereas the homomeric

eukaryotic ACCase is a large multidomain protein. Thus, most dicot species tolerate ACCase-inhibiting herbicides well, but most grass species are susceptible, meaning that ACCase herbicides control only grass weed species [51]. Multiple forms of eukaryotic ACCase are present in some grasses, which differ in herbicide sensitivity [52]. This is the primary basis for selectivity of these herbicides between grasses and dicots. Some grass species, including some cereal crops, are tolerant of these herbicides based on their ability to metabolize the herbicides to inactive compounds [53]. In addition, some grasses are tolerant due to an insensitive form of ACCase [54, 55].

Hedgehog dogtail (*Cynosurus echinatus*) is an annual grass, native to Europe, additionally broadly conveyed in North and South America, South Africa, and Australia. Two hedgehog dogtail biotypes, one diclofop-methyl (DM) safe and one DM vulnerable, were examined in detail for exploratory measurements reaction resistance components. The digestion system of 14CDM, D-corrosive, and D-conjugate metabolites were recognized by thin-layer chromatography. The acetyl-CoA carboxylase *in vitro* tests demonstrated that the objective site was exceptionally touchy to aryloxyphenoxy propanoate, cyclohexanedione, and phenylpyrazoline herbicides in the *Cenchrus echinatus* susceptible biotype, provided the resistant biotype was coldhearted to the already specified herbicides. DNA sequencing concentrates affirmed that *Cenchrus echinatus* cross-imperviousness to acetyl-CoA carboxylase inhibitors has been presented by particular acetyl-CoA carboxylase two-fold point transformations Ile-2041-Asn and Cys-2088-Arg [48].

The results of enzyme inhibition studies suggest several distinct altered forms of ACCase associated with different levels of resistance to various ACCase inhibitors [56]. Mostly, resistance to aryloxyphenoxy propanoate and cyclohexanedione herbicides is owing to a mutation in the objective enzyme, making it lesser susceptible to blockage by these herbicides. The results of enzyme deterrence investigates propose some different modified figures of acetyl CoA carboxylase correlated with various measures of resistance to distinct acetyl CoA carboxylase inhibitors. In contrast, a second biotype was very resistant to sethoxydim (R/S I50 ratio of 420), but had only a low level of resistance to other AOPP and CHD herbicides [57]. A similar pattern was observed in a *Setaria faberi* biotype from Iowa and in a sethoxydim-resistant corn line selected in tissue culture [58, 57]. A third pattern of resistance, conferring high-level resistance to fluazifop and lower levels of resistance to other AOPP and CHDs, has been found in a biotype of *Eleusine indica* from Malaysia [59], a *Lolium rigidum* biotype from Australia [60]. In a fourth category, some biotypes are resistant to AOPP herbicides but not to CHDs. These include *L. rigidum* biotype a VLR69 from Australia [61], a *Lolium multiyorum* biotype from Oregon, the USA [62], and *Avena fatua* biotype UM33 from Manitoba, Canada [63]. Similar groupings of resistant biotypes have been proposed in Ref. [64] according to entire plant cross-resistance templates to aryloxyphenoxy propanoate and cyclohexanedione herbicides in *Avena fatua* biotypes from Canada. Because of the two different acetyl CoA carboxylase genes in the weed grasses, this plant family encodes both cytosolic and plastidic figures of the acetyl CoA carboxylase. The target form of acetyl CoA carboxylase for aryloxyphenoxy propanoate and cyclohexanedione herbicides is the plastidic form, and in fact, this form of acetyl CoA carboxylase is modified in resistant weed biotypes [65]. Generally, the different patterns of resistance may be endowed by separate mutations in the gene for

plastidic ACCase. Some reports indicate that at least one of the mutations is located in the carboxyltransferase region, toward the C terminal end of plastidic ACCase [66, 67]. Further molecular analysis is required to confirm the identity of this and other mutations responsible for resistance to these herbicides [15].

3.1.5. Resistance to AHAS (ALS)-inhibiting herbicides

Acetolactate synthase (ALS) is the first enzyme in the biosynthetic for the branched-chain amino acids, such as valine, leucine, and isoleucine. A large number of herbicides, for example, sulfonylurea (SU), imidazolinone (IMI), triazolopyrimidine, pyrimidinyl-thiobenzoates, and sulfonyl-aminocarbonyl-triazolinone effect on acetohydroxyacid synthase (AHAS) catalyzes the formation of both aceto-hydroxybutyrate and acetolactate [68]. The vast AHAS-inhibiting herbicide resistance literature has been thoroughly reviewed [69, 70], so here, we are focusing on last expansions. It was rapidly established that AHAS herbicide-resistant plants could have a mutant, resistant AHAS enzyme [71, 58], and reports of resistant AHAS in many weeds followed. At Pro-197, 11 amino acid substitutions can endow AHAS herbicide resistance [51]. Although faster herbicide detoxification is a mechanism in some biotypes, in most cases, resistance to ALS and AHAS herbicides is endowed by target-site mutations [11, 72]. Target-site-based ALS resistance is due to point mutations that occur within discrete conserved domains of the ALS gene [11]. Most resistance mutations occur at the Pro-197 position, including one based on a double mutation [32]. Pro-197 mutations confer a high level of resistance to sulfonylurea herbicides, but low or no cross-resistance to imidazolinone herbicides. The Trp591 to Leu mutation confers high levels of resistance to all ALS inhibitors, whereas the Ser670 to Asp and Ala122 to Thr mutations confer a high level of resistance to imidazolinones but little change in sensitivity to sulfonylurea and triazolopyrimidine herbicides [73, 74].

As with triazine resistance, double mutations have been identified that confer higher levels of resistance to ALS inhibitors [75, 76]. Imidazolinone-resistant corn and wheat lines were selected *in vitro* in cell cultures or following seed mutagenesis resistant to various classes of ALS inhibitor [77, 66]. The development of selective uses for these herbicides may result in added selection pressure for resistant weeds, emphasizing the need for careful herbicide management to maintain the long-term usefulness of these herbicides [78, 15].

3.1.6. Resistance to PSII-inhibiting herbicides

Triazine and phenylurea herbicides do so by binding to the plastoquinone (PQ)-binding site on the D1 protein in the PS II reaction center of the photosynthetic electron transport chain. The D1 protein is coded by the *psb*A gene. PS II herbicide has two major consequences: (a) a shortage of reduced NADP`, which is required for CO2 fixation; and (b) the formation of free radicals which cause photooxidation of important several molecules such as chlorophylls and unsaturated lipids in the chloroplast. Triazine (simazine) resistance in weeds (*Senecio vulgaris*) was first identified in the late 1960s [24, 79, 80]. Since then, resistance to triazine herbicides has been reported in several weed species that many of them have developed in corn monocultures in the North America and Europe [81, 82]. Most s-triazine resistant biotypes show a high level of cross-resistance to other s-triazine herbicides, a lower level of resistance

to as-triazinones, but no cross-resistance to phenylurea herbicides [83]. In almost all cases, a Ser264 to Gly mutation in the D1 protein is responsible for conferring resistance in weed biotypes [79]. QB may yet availability this site and transmits electrons to the cytochrome b6/f complex from the PS II reaction center, while the herbicide is absent. Ser264 to Gly mutation has no impact on the affinity of substituted urea herbicides and other PS II electron transport inhibitors, although it decreases the binding affinity of s-triazine and as-triazine herbicides to the D1 protein [39]. Biotypes containing this mutation exhibit a resistance factor of 1000 at the binding site on the D1 protein and 100 at the whole plant level [25, 84]. A resistant biotype of *Portulaca oleracea* has a high level of resistance to atrazine and to linuron, which through a Ser264 to Thr mutation which is the first reportage about D1 Ser264 to Thr mutation in higher plants selected under field conditions. Formerly, in tobacco and potato, this mutation had only been elected through tissue culture [85–87]. Both the Ser264 to Gly and Ser264 to Thr mutations reduce the efficiency of photosynthetic electron transport in the absence of herbicide [88, 89]. Resistance mutations can occur at positions other than Ser264, and mutations at Ser264 do not necessarily confer herbicide resistance. Molecular analysis has revealed that mutations at or close to positions Ser264, Phe265, Phe255, and His215 can affect the binding of PQ or herbicides and play an important part in the development of resistance [79, 11]. These results indicate that a mutation at Ser264 does not necessarily lead to resistance. Several mutations at positions other than Ser264 have been identified that confer resistance to triazine herbicides. Recently, a Val219 to Ile mutation has been identified in *Poa annua* populations resistant to metribuzin and diuron [90]. Val219 to Ile and Ala251 to Val or Thr mutations, without a change at Ser264, were suggested to be responsible for triazine resistance in various cell culture lines of *Chenopodium rubrum* [91]. In Ref. [92], Trebst has discussed amino acid changes between positions 211 and 275, including Phe211 to Ser, Gly256 to Asp, and Leu275 to Phe that confer herbicide resistance in various organisms. Some researchers reported a Ser268 to Pro mutation in soybean cell culture that confers a high level of resistance to both triazine and phenylurea herbicides [93]. Negative cross-resistance has been reported in some instances in which a triazine-resistant biotype is hypersensitive to phenylureas and other PS II-inhibiting herbicides [25, 94]. A *Chlamydomonas* mutant (Phe255 to Tyr) displayed negative cross-resistance to diuron and atrazine-resistant biotypes of *Amaranthus cruentus*, and *Amaranthus hybridus* showed negative cross-resistance to bentazon and pyridate [92, 95].

3.1.7. Resistance to auxin-type herbicides

Auxin-type herbicides that mimic the endogenous auxin indole acetic acid (IAA) are among the oldest weed control products in use today. Nevertheless, the molecular binding site has not been recognized and the correct mechanism of action is not excellent realized, despite years of intense study. These compounds can motivate protein biosynthesis, and on the other hand, inhibit cell division and growth at low and higher concentrations, usually in the meristematic regions, respectively. The cell wall plasticity and nucleic acid metabolism primarily affect these compounds. The most broadleaf weeds well control through synthetic auxins [96]. Resistance to these herbicides is uncommon, considering their history of intensive use in cereal cropping systems [97].

3.2. Non-target-site herbicide resistance

Non-target-site-based resistance (NTSR) can confer unpredictable cross-resistance to herbicides. The non-target-site-based resistance mechanisms can interfere with herbicide penetration, translocation, and accumulation at the target site. NTSR is a part of the plant stress response. As such, NTSR is a dynamic process unrolling over time that involves "protectors" directly interfering with herbicide action, and also regulators controlling "protector" expression. NTSR is thus a quantitative trait. Infiltration of the herbicide into the plant and translocation to its site of action, reposition of the herbicide at its site of action, and binding of the herbicide to its target protein are three stages of herbicide action [8].

3.2.1. Decreased herbicide infiltration and displacement

Decrease in infiltration of herbicide has been reported in resistant weeds and crops for every main herbicide modes of action, that is, glyphosate [6, 98] acetolactate synthase, and acetyl CoA carboxylase inhibitors [99, 100]. This is owing to variations in the some physical and chemical attributes such as physical and chemical properties of the hull in resistant weeds and crops that bring a decline in the maintenance of the herbicides dilution on the foliage and/or a decrease in the influence of herbicides infiltration via the hull. Decrease in dislocation of herbicides has been investigated by other researchers [10, 51]. This phenomenon initiates some limitation in the move of the herbicide in the weeds or crops and in some cases the herbicide compartmenting. Decreased herbicide infiltration and displacement is a main mechanism of resistance to several herbicides, for example, paraquat and glyphosate. It has been made clear that depend on the weed or crop specie, or on the single weed or crop, non-target-site herbicide resistance toward paraquat inclusive the limited translocation through xylem, sequestration in the cell wall or in the vacuole and decreased uptake into the leaf cells [51, 101]. Limited translocations through the xylem and/or the phloem and/or quick sequestration to the vacuole are events, which occur through the non-target-site herbicide resistance toward glyphosate [6, 51, 102].

3.2.2. Enhanced herbicide degradation

Enhanced herbicide degradation is certainly the most studied aspect of NTSR. Herbicide degradation is a multistep process involving the coordinated action of several types of enzyme which have several stages. These stages involved the transformation of molecule of herbicide to some hydrophilic metabolite (stage I), the conjugation of hydrophilic metabolites into a plant acceptor molecule (such as a sugar) (stage II), and the exportation of the metabolite(s) into the vacuole and/or the cell walls after additional conjugation, cleaving, and/or oxidation stages [8, 103, 104].

3.2.3. Conservation versus the parallel recompense of herbicide action

This type of mechanism has been best studied in the case of *Alopecurus myosuroides* NTSR to ACCase repressors. Acetyl-CoA carboxylase (ACCase) inhibitors—herbicides, by interrupting biosynthesis of fatty acids, bring the extrication of active oxygen species that harm the

ingredients of cells. Non-target-site-based resistance is mostly conferred through an increase in the expression of peroxidases that support the cells versus oxidative harm in several resistant plants. Hereon, non-target-site-based resistance is not case to an increase in degradation of herbicide in resistant species than sensitive species [8, 101, 105, 106].

4. Methods of identify resistance

4.1. Target-site resistance

The primary herbicide-resistant weeds were seriously examined in the 1980s–1990s. As a rule, resistance was given by means of TSR components controlled by prevailing alleles at a nuclear locus [7, 51, 107–109].

To date, nuclear monogenic control of TSR has been identified to herbicide groups A, B, K1, K2, E, and G (**Figure 1**), while legacy of TSR to triazine herbicides (C) is cytoplasmic. TSR is particularly across the board to herbicides in groups A, B, and C [7, 51, 108, 109]. Late advances demonstrate that atomic monogenic TSR is less basic than already suspected. Albeit most TSR cases will be surely given by overwhelming or semi-predominant alleles [7, 19], latent control of TSR has been accounted for imperviousness to herbicides in gathering K

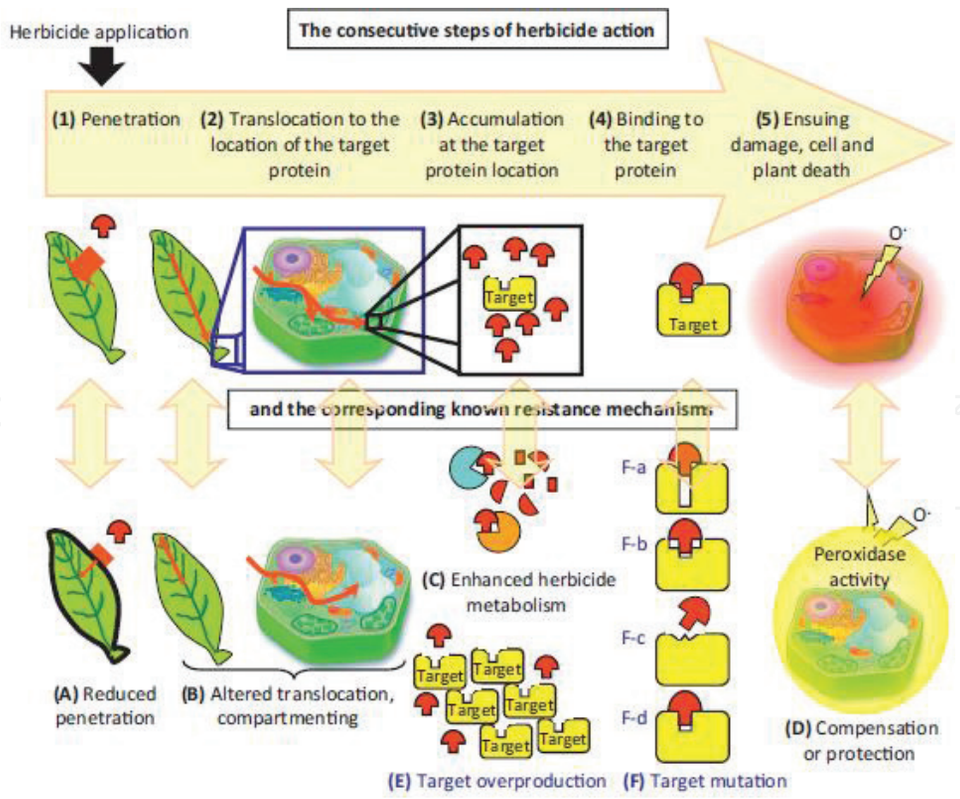

Figure 1. The action of herbicides following their application and the resistance mechanisms identified in weeds that correspond to each action step [122].

[110]. TSR is to a great extent invested by changes in the 3D structure of the herbicide target protein and in the dissemination of polar gatherings at positions significant for the security of herbicide official to the protein (**Figure 1**) [111, 112]. Auxiliary changes are for the most part because of amino-corrosive substitutions at one of a few conceivable positions on the herbicide target protein [7, 83, 108, 113]. A few substitutions giving resistance are conceivable at a given vital codon: upwards of 12 substitutions blessing resistance have been recognized at codon 197 in acetohydroxyacid synthase, the objective protein of gathering B herbicides [7]. The size of diminishment in proclivity of an herbicide for its coupling site depends both on the basic change in the objective protein and on the herbicide particle. Contingent upon the herbicide, a given basic change in the objective protein can give high or direct resistance [114, 115] or, in uncommon examples, an expansion in affectability to the herbicide (**Figure 1**) [110]. Along these lines, as opposed to the finishes of early reviews, the rising picture of TSR is not in highly contrasting, but rather in shades of dark [116].

It has been made clear that complex hereditary changes in weeds, including the erasure of a whole codon, progressive amino-corrosive substitutions coming about because of two sequential nucleotide substitutions at a similar codon, gathering of two amino-corrosive substitutions at particular codons that expanded the resistance level contrasted with a solitary transformation, and an expansion in amalgamation of the objective protein [117–119]. These systems seem from now on occasional in weeds, potentially because they include hereditary variations with a low likelihood of outward. In any case, the parallels with TSR to fungicides and insecticides propose that future work into the hereditary qualities of TSR to herbicides may uncover more perplexing components. Advancement of TSR is expected to adjust to the specific breadth model of adjustment [120] where a solitary valuable change of vast impact permits the underlying survival of mutants and after that spreads rapidly due to positive determination [121]. Basic populace hereditary models have demonstrated accommodating to coordinate the impacts of these developmental calculates the past and to evaluate the adequacy of different administration techniques in diminishing the likelihood of, and time to, resistance advancement [122].

Most DNA-based examinations for herbicide resistance depend on the polymerase chain reaction (PCR) to amplify a DNA sequence of interest from the milieu of DNA that is not of interest. Most standard "genomic" DNA extraction strategies yield DNA from the nuclear, chloroplastic, and mitochondrial genomes, and hence are appropriate for an extensive variety of downstream molecular analyses, including PCR. DNA can be removed from a wide range of plant material. In the absence of fresh tissue, high-quality DNA can also be extracted from preserved material [13].

DNA can as well as be synthesized from messenger RNA (mRNA) utilizing a reverse-transcriptase enzyme. This enzyme synthesizes DNA complementary to RNA (cDNA) from the 39 end of a primer hybridized on the RNA strand, utilizing the RNA strand as a template. cDNA is of specific interest when working on genes with complex intron–exon structure, because, like mRNAs, cDNAs do not contain introns [123]. The polymerase chain reaction (PCR) can hugely reproduce a given DNA district (amplicon) from little amounts of DNA. The easiest way to acquire sequence data for a given gene is to use the PCR amplicon as a template for

Sanger sequencing [13, 124]. In many studies, these approaches were used to uncover TSR in weeds [125–131].

4.2. Non-target-site resistance

Recognizing alleles of non-target-site-based resistance requires the identification of alleles specific for resistant genotypes while contrasted with sensitive genotypes, and to eliminate "false positives." These alleles are diverse in both genotypes (resistant and susceptible), however, do not involve in non-target-site-based resistance. In plant genomes, there are numerous alleles reported to be associated with non-target-site-based herbicide resistance. Alleles associated with quantitative characteristics are mostly identifies using genetic marker approaches (quantitative trait loci (QTL) mapping) [132]. QTL mapping is intricate, time consuming, and not easily applied to natural or field populations of nonmodel organisms such as weeds [133]. Another approach utilized for identification of alleles dedicating quantitative properties is to interrupt or imitate the phenotype of interest through genetic transformation [134]. Owing to the recent technical and scientific "omics" revolution, the genetic basis of quantitative characteristics, such as NTSR, can be explained even in nondemonstrate species, for example weeds. To accomplish this objective, three stages ought to be completed (**Figure 2**).

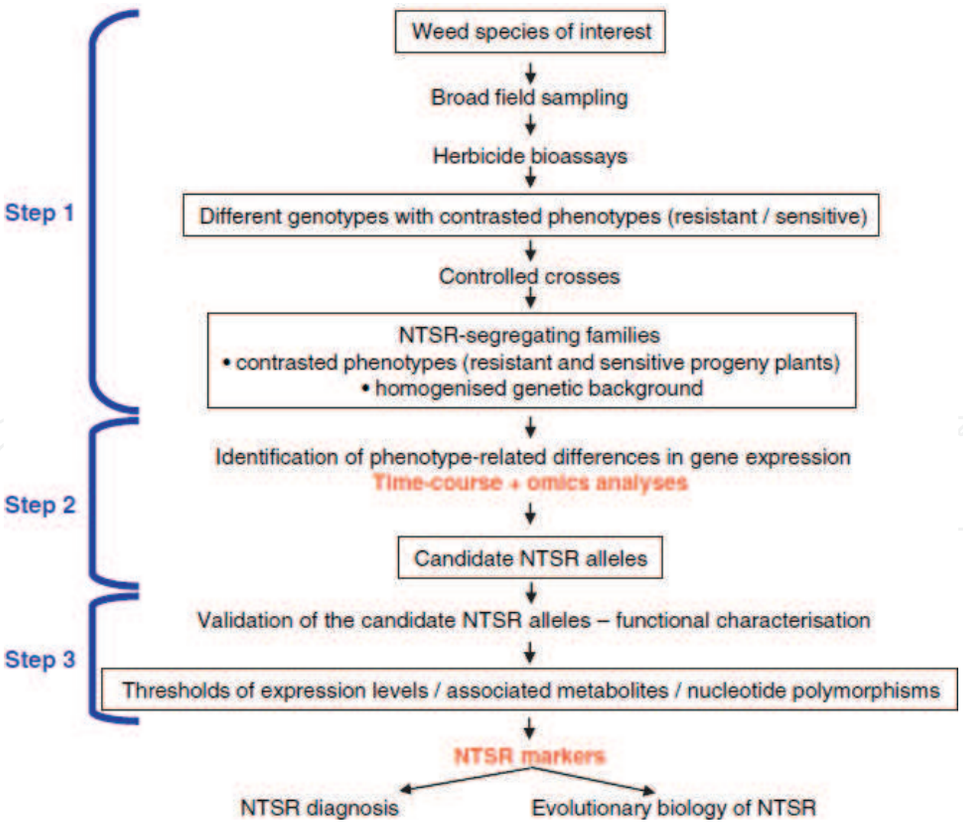

Figure 2. Three-step procedure to identify NTSR alleles [8].

5. Cytochrome P450 monooxygenases (P450S) and evolved herbicide resistance

P450s are one of the largest super families of enzymes. Plants have the most noteworthy number of P450 genes. It is well demonstrated that tolerance to several modes of action to some herbicides is associated with Cyt P450 mediated enhanced metabolism. Cytochrome P450s in plants synthesize sterols, fatty acid derivatives, and hormones and in some cases, these are involved in plant secondary metabolism. Usually, plant cytochrome P450s are limited in the endoplasmic reticulum (in a few cases to plastid membranes). When a vast variety in plant metabolism catalyzes by cytochrome P450s, the role of cytochrome P450s is often hydroxylation or dealkylation in the herbicide alteration. Several plant cytochrome P450s will metabolize some herbicides to further inactivated productions so that their phytotoxicity will decrease or alter. Mostly, this process occurs by conjugation to glucose and subsequent transport into the vacuole. [36, 46, 135]. As crops can P450 metabolize many different herbicides, their use on large weed populations is a strong selection pressure for weed individuals possessing the same ability. Indeed, in weeds, P450-based herbicide resistance is a very threatening resistance mechanism because P450 enzymes can simultaneously metabolize herbicides of different modes of action, potentially including never-used herbicides [136, 137]. Subsequently, *in vivo* studies on herbicide metabolism and P450 inhibitors in resistant biotypes showed that P450s catalyzed enhanced rates of metabolism of several herbicides [138–140]. In addition to *L. rigidum* and *A. myosuroides*, the evolution of resistance due to P450-catalyzed enhanced rates of herbicide metabolism has been demonstrated in resistant biotypes of a further nine weed species [57, 141]. Cytochrome P450s can metabolize low dose of diclofop-methyl in some susceptible biotypes of *L. rigidum* and therefore the weeds were treated at a dose bringing around 50% mortality. Some survivors were grown for producing seeds to create the next generation, and in this direction, the selection was repeated. Non-target-site resistance was progress of high level in lonely three generations [142]. Importantly, there was concomitant evolution of cross-resistance to other P450-metabolizable herbicides of different modes of action [85, 88]. In *L. rigidum*, evolved P450-based herbicide resistance can be correlated with a fitness cost [143, 144]. Up to now, slight data are obtained through biochemical investigation to determine P450-based herbicide resistance in some evolved resistant weed species. Cytochrome P450 microsomes which degrade herbicides have not been successfully isolated from resistant *A. myosuroides* and *L. rigidum*, while they have been successfully isolated from resistant *E. phyllopogon* [145]. Isolated 16 P450 genes from a resistant *L. rigidum* biotype were not imputed to herbicide metabolism [76, 146]. One of three full-length P450s, CYP71R4, were gained from resistant *L. rigidum* biotypes metabolized a PSII herbicide, while expressed in yeast [147]. P450 proteins can share as little as 16% amino acid identity, and there are more than 2000 plant P450 sequences in the P450 database. Reportages about P450-based evolved herbicide resistance in grass weed species has often been more than dicot species, whereas dicot weed species have less P450 genes toward grass weed species. This fact reflects the attitude of some investigate to test only for target-site-based resistance [17].

6. Glutathione S-transferases and evolved herbicide resistance

Glutathione S-transferases (GSTs) which catalyze the conjugation of glutathione to variety of hydrophobic, electrophilic substrates, are multifunctional enzymes. Glutathione S-transferases (GSTs) have a special role in protecting the plant from oxidative stress (e.g., from reactive oxygen species), thus functioning as protective mechanism [16]. Glutathione S-transferases (GSTs) detoxify several herbicides in some crop and weed species. These enzymes play a role in stress response [148–150]. Glutathione-conjugated herbicides can be sequestered in the vacuole or exuded via root tips [149, 151]. Herbicide-metabolizing GSTs have been purified and characterized from several crops [150, 152]. Some studies such as molecular modeling, mutagenesis studies, and also the resolution of the 3D structure of plant GST (including herbicide-induced GST) provide an understanding of the molecular basis of GST-catalyzed herbicide binding and how single amino acid substitution(s) can improve GST catalytic efficiency and affect substrate specificity for herbicides and xenobiotics [153–155]. Because the Glutathione S-transferases (GSTs) catalyze the conjugation of triazines to glutathione through their high activity, these herbicides are selective for corn. This feature cause to widespread utilize of triazines can elect some weeds with glutathione S-transferases capable to eliminate them. Actually, in some weed species such as *Abutilon theophrasti*, developed GST-intervened triazine herbicide resistance has been observed [49, 156]. More researches demonstrated that enhanced activity of glutathione S-transferases is owing to higher catalytic susceptibility compared with overexpression enzyme or presence of a novel glutathione S-transferases [157]. This shows a conceivable transformation (mutation) in the gene of glutathione S-transferase gene which could better herbicide binding and so glutathione S-transferase catalytic performance. Resistance to atrazine as a singular nuclear gene with sectional predomination is inherited in this biotype [5]. It was demonstrated that in a resistant *Echinochloa phyllopogon* biotype, fenoxaprop-*p*-methyl resistance can be due to glutathione-herbicide conjugation [80]. Investigates with multiple resistant *A. myosuroides* biotypes with increased P450-catalyzed herbicide metabolism also show that they have higher GST activity [149, 158, 159]. Generally, GST enzymes can play both a direct role and an indirect role in evolved herbicide resistance [17].

7. Taxonomic effects in herbicide-resistant weeds and deployment of resistant crops

Evolved herbicide resistance (EHR) has become a threat to agriculture around the world [12, 160, 161]. Evolved herbicide resistance in weeds was initially reported in 1970 and generally considered during the 1970s throughout the 1990s [80, 162]. The rate of instances has precipitated significantly during those decades. Up to now, the advancement of imperviousness to various herbicides with various mode of action has additionally been detected inside various weed species [51]. The detection of resistance to glyphosate, and the introduction of transgenic glyphosate-resistant crops in the 1990s, also the recent expansion of cases of evolved resistance to glyphosate in weeds, likely because to greater glyphosate usage, have inspired a renewal of interest and resurgence of research into this phenomenon [113, 163].

In spite of four decades of research on evolved herbicide resistance, it is unclear wherefore a few weeds develop resistance quicker than others. Baker's list of specifications which may be anticipated in the "ideal weed" is excellent recognized; one may anticipate that weeds with evolved herbicide resistance will have a subset of these qualities [164]. This perception was ascribed to chance, as lots of resistant weeds among the world's worst weeds, are widespreading, and happen in many cropping systems [165–167]. Well before evolved herbicide resistance was detected, inheritable variability, breeding system, reproductive valence, and population size were predicted to associate with development of herbicide resistance [168]. Other plant variables can influence the development of resistance, including change recurrence, generation time, and compatibility in lack of the herbicide, pliancy, and soil seed repository, and in addition, method of legacy of resistance, size of population, seed dormancy, and gene flow by pollen and seed [121, 169]. Whenever these factors have been tested in models predicting evolution of resistance, few have been examined empirically [168, 170].

In spite of relatively cohesive internally of taxonomic families, there are usual differences in terms of ecological properties among them; in fact, evolved herbicide resistance does not occur randomly among weed or crop species. Generally, depending on perceptions and reportages of the tendency for resistance to evolve within certain genera or species, evolved herbicide-resistant weeds are distinct ecologically and taxonomically toward other weeds [171]. Some researchers found the same trends for subsets of weeds with EHR to acetolactate synthase (ALS), photosystem II (PSII), and 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase-inhibitor herbicides and with multiple resistances. Comparing taxonomic and life history traits of weeds with EHR to a control group ("the world's worst weeds"), we found weeds with EHR significantly overrepresented in certain plant families and having certain life history biases [171].

8. GM crops

Herbicide-resistant crops (HRCs), sometimes called herbicide-tolerant crops, are crops made resistant to herbicides either by transgene technology or by selection in cell or tissue culture for mutations that confer resistance [172, 173]. Two techniques have been for all intents and purposes connected to generation of HR plants by hereditary building monetarily are: the presentation of the quality encoding the herbicide-inactivating catalyst, the presentation of the mutant, or outside quality. The advance in quality cloning and quality exchange, particularly utilizing *Agrobacterium tumefaciens*, has made hereditary building the most well known at present [174].

8.1. The gene encoding the herbicide-inactivating enzyme

This strategy has been most widely applied for the production of HR crops. The key step is to clone the gene encoding a herbicide-inactivating or detoxifying enzyme with high specificity and efficiency. Glufosinate-resistant crops sold as Liberty Link were produced by the introduction of the bar gene encoding the glufosinate-inactivating enzyme. The *bar* gene was

cloned from Streptomyces hygroscopicus which produced bialaphos, the precursor of glufosinate (phosphinothricin). The *bar* gene encodes phosphinothricin-N-acetyl-transferase (PAT) which acetylates bialaphos to an inactivated form and prevents autotoxicity of bialaphos in the bacterium [174].

Bromoxynil-resistant crops sold as BXN were produced by the introduction of the *bxn* gene encoding the bromoxynil-inactivating enzyme [175]. However, the *gox* gene encoding the glyphosate-inactivating enzyme was also introduced into some plant species, possibly to enhance the level of resistance [176]. The gene encoding the 2,4-dichlorophenoxyacetic acid (2,4-D)-inactivating enzyme was also cloned from a soil bacterium because 2,4-D was readily inactivated in soil [177]. *Alcaligenes eutrophus*, thus selected, utilized 2,4-D as the sole source of carbon. The *tfd*A gene from the bacterium converts 2,4-dichlorophenoxyacetic acid (2,4-D) to 2,4-dichlorophenol. An option technique is to use the quality encoding the catalyst required in the imperviousness to more than one herbicide, for example, glutathione S-transferase and cytochrome P-450 [178].

Resistance types of EPSPS from petunia or Salmonella, conveying Gly96 to Ala or Pro101 to Ser changes, were assessed in early transgenic plants. In spite of the fact that these changes do give imperviousness to glyphosate, the reactant properties of the modified protein are hindered, which decreases the force of the plants without herbicide. The popularized glyphosate-safe harvests contain the *Agrobacterium* CP4 EPSPS quality [176]. Focusing on the CP4 quality to the chloroplast presents an abnormal state of imperviousness to glyphosate sans the negative impacts connected with the single transformation EPSPS qualities portrayed previously. In some transgenic edit cultivars, glyphosate resistance is presented by a mix of the CP4 quality and a bacterial oxidoreductase quality that detoxifies glyphosate. An option wellspring of glyphosate resistance for transgenic plants is an EPSPS quality conveying two separate changes in a similar district of the quality (positions 101, 102 as well as 106) [179]. This two-fold mutant quality has not been presented in any marketed safe yields. Glyphosate resistance can likewise be founded on intensification of the EPSPS quality, prompting to expanded levels of transcript creation and EPSPS action [180–182]. Essentially, adequate EPSPS is created to titrate out the glyphosate, leaving an overabundance of chemical that remaining parts practical. This has been appeared in plants chose in tissue culture or through repetitive choice. Now and again overexpression is lost when the choice weight is expelled or when plants are recovered; in others, the quality has all the earmarks of being steady in recovered plants and their descendants. Be that as it may, this component has not been utilized to create glyphosate-safe yields [15].

8.2. Mutant or foreign gene encoding the target enzyme with low affinity to the herbicide

This strategy is applicable to the production of any HR crops. But it was applied to commercial HR crops, which have been restricted to glyphosate-resistant crops sold as Roundup Ready. Generally, when an enzyme with a high herbicide binding constant was produced by a mutant gene, its enzymological characteristics were found to be unfavorable for the maximal enzyme activity leading to decreased growth and fitness of the plants transformed with

this gene. It was known that EPSPSs from some bacteria were naturally resistant to glyphosate. EPSPS from *Agrobacterium* sp. strain CP4 was selected with high glyphosate-resistance and catalytic efficiency in the presence of glyphosate. The CP4 EPSPS gene was cloned from the bacterium and used for the production of Roundup Ready crops such as soybean, canola, cotton, maize, and sugar beet [51]. The target enzyme of sulfonylurea, imidazolinone, and triazolopyrimidine herbicides is acetolactate synthase (ALS). Various resistant ALS genes were cloned from tobacco [183] and *Arabidopsis thaliana* [184]. These gene products showed different levels of resistance to sulfonylureas, imidazolinones, and triazolopyrimidines [15]. These resistant ALS genes were introduced into plants individually, or in combination, and conferred resistance to these herbicides. Though some of these genes conferred resistance even at field trials, these genes have not been used for commercialization [185].

8.3. Novel tools for development of herbicide-resistant crops

Plant cells have three genomes and, in some plant seeds, two of these genomes are transformable: the nuclear genome and the genome of the plastids (chloroplasts). The plastid genome of photosynthetically active seed plants is a small circularly mapping genome of 120–220 kb, encoding 120–130 genes. It can be engineered by genetic transformation in a (still relatively small) number of plant species, and this possibility has stirred enormous interest among plant biotechnologists. There are considerable attractions associated with placing trans-genes into the plastid genome rather than the nuclear genome. First and foremost, the high number of plastids per cell and the high copy number of the plastid genome per plastid offer the possibility of expressing foreign genes to extraordinarily high levels, often one to two orders of magnitude higher than what is possible by expression from the nuclear genome [186, 187]. Second, transgene integration into the plastid genome occurs exclusively by homologous recombination, making plastid genome engineering a highly precise genetic engineering technique for plants. Third, as a prokaryotic system that is derived from a cyanobacterium acquired by endo-symbiosis, the plastid genetic system is devoid of gene silencing and other epigenetic mechanisms that interfere with stable transgene expression. Fourth, similar to bacterial genes, many plastid genes are arranged in operons offering the possibility to stack transgenes by arranging them in artificial operons. Finally, plastid transformation has received significant attention as a superb tool for transgene containment due to the maternal mode of plastid inheritance in most angiosperm species, which drastically reduces transgene transmission through pollen [188, 189]. Since the development of plastid transformation for the seed plant tobacco (*Nicotiana tabacum*) more than 20 years ago [64, 190], the community has assembled a large toolbox for plastid genetic engineering and also made some progress with developing plastid transformation protocols for additional species. Unfortunately, plastid transformation is still restricted to a relatively small number of species and not a single monocotyledonous species (including the cereals representing the world's most important staple foods) can be transformed. Thus, developing protocols for important crops continues to pose a formidable challenge in plastid biotechnology and significant strides forward are likely to require conscientious efforts and long-term investments in both the academic and the industrial sectors [26].

9. Conclusion

Herbicide-resistant weeds are a crucial topic in agriculture. Growers need to interchange weed management techniques thus prolonging the development of herbicide-resistance in weeds. Defiantly, the important and effective approaches to manage the herbicide-resistant weeds are prevention of weed emergence, integrated application of all available options to weed control, and rotate herbicides with different modes of action.

Nowadays, Herbicide-resistant crops have transformed the weed management strategy of many growers. Herbicide-resistant or - tolerant crops have helped farmers to manage weeds more comfortable to meet the growing demands for human food, fiber, and fuel and animal feed. The advent and development of herbicide-resistant crops has provided conditions to minimize production losses because of weed infestation. Generally, growers need intelligent management approaches to maximize the long-term benefits of this technology and reduce weed shifts to difficult-to-control and herbicide-resistant weeds.

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