Chapter 2

Weed Resistance to Herbicides

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Additional information is available at the end of the chapter

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Abstract

Unfortunately, herbicide resistance developed shortly after the introduction of the herbicides 2,4-D in 1957. According the herbicide resistance mechanisms, all processes can be grouped as follows: target-site resistance, non-target-site resistance, cross-resistance and multiple-resistance. Target-site resistance is generally due to a single or several mutations in the gene encoding the herbicide-target enzyme, which, in turn, decreases the affinity for herbicide binding to that enzyme. Non-target-site resistance is caused by mechanisms that reduce the amount of herbicidal active compound before it can attack the plant through the reduced absorption or altered translocation, increased herbicide sequestration or enhanced herbicide metabolism. Cross-resistance means that a single-resistance mechanism causes resistance to several herbicides with some mode of action. Multiple-resistance is a situation where two or more resistance mechanisms are present within the same plant, often due to sequential selection by herbicides with different modes of action. Currently, herbicide resistance has been reported in 478 weed biotypes (252 weed species) in 67 countries. Many of those biotypes are resistant to acetolactate synthase (ALS) inhibitors, PS II inhibitors, ACC-ase inhibitors and EPSPS inhibitors. Strategy for herbicide-resistance weed management must involve all the available preventive, cultural, mechanical and chemical measures for effective, safe and cost-effective weed control.

Keywords: weed, herbicide, resistance, management

1. Introduction and general overview of resistance

Since the introduction of 2,4-D as a first selective herbicide in 1947, herbicides have had a major positive impact on weed management in all over the world. Unfortunately, herbicide resistance developed shortly after the introduction of the herbicides. The phenomenon of resistance can be defined as the decreased response of a species' population to herbicide [1].

It is also defined as a 'survival of a segment of the population of a weed species following an herbicide dose lethal to the normal population' [2]. In addition, resistance can be defined as 'the inherited ability to survive treatment by a herbicide' [3], or it is a 'phenomen which occurs as a result of heritable changes to biochemical processes that enable weed species survival when treated with a herbicide' [4].

Weed resistance to herbicides is a normal and predictable outcome of natural selection. In that context, rare mutations that confer herbicide resistance exist in wild/weed populations before any herbicide introduction. These mutations increase over time after each herbicide application until they become predominant at what time the weed population is called resistant [5]. The first confirmed herbicide-resistant weed species was *Senecio vulgaris* that had developed resistance to PS II inhibitors (atrazine and simazine) after the herbicides had been applied once or twice annually for 10 years [6]. Therefore, about 30-resistant weed populations have been confirmed within the first decade, mostly in N. America and W. Europe [7]. Some weed species, such as *Lolium rigidum*, *Echinochloa crus-galli* var. *crus-galli*, *Poa annua*, *Alopecurus myosuroides*, *Echinochloa colona*, *Eleusine indica*, *Amaranthus* sp., etc. have a high affinity to develop resistance especially due to their congenital genetic variability. Additionally, herbicides of different chemical groups and different modes of action (e.g. sulfonylurea and synthetic auxins) can greatly differ in their risk levels for resistance. On the other hand, different chemical groups with the same mode of action such as herbicide inhibitors of acetolactate/acetohydroxyacid synthase (ALS/AHAS) (sulfonylurea, pyrimidinyl(thio)benzoate, sulfonylaminocarbonyl-triazolinone, imidazolinone) can also be distinguished in their risk level for resistance.

Currently, herbicide resistance has been reported in 478 weed biotypes (252 weed species) in 67 countries. Many of those biotypes are resistant to ALS inhibitors, B/2 (97 dicots + 62 monocots), PS II inhibitors (C1/5 = 51 + 23, C2/7 = 10 + 18, C3/6 = 3 + 1), ACC-ase inhibitors, A/1 (48 monocots) and EPSPS inhibitors, G (19 + 17). The highest number of confirmed resistant weed species belongs to the families: *Poaceae* (80 species), *Asteraceae* (39), *Brassicaceae* (22), *Cyperaceae* (12), *Amaranthaceae* (11), *Scrophulariaceae* (9), *Chenopodiaceae* (8), *Alismataceae* (7), *Polygonaceae* (7) and *Caryophyllaceae* (6). According to the number of active ingredients (a.i.), those four sites of action participate in the next relation: 50 a.i. from ALS inhibitors, 24 a.i. from PS II inhibitors, 15 a.i. from ACC-ase inhibitors and 2 a.i. from EPSPS inhibitors. Atrazine (PS II inhibitors) is an active ingredient, which was confirmed by the greatest number of weed resistant species (66), the second is imazethapyr (44), followed by tribenuron-methyl (43), imazamox (37), chlorsulfuron (36) metsulfuron-methyl (35), glyphosate (34), iodosulfuron-methyl-sodium (33), fenoxaprop-P-ethyl (31), simazine (31), bensulfuron-methyl (29), thifensulfuron-methyl (27), fluazifop-P-bityl (25), pyrazosulfuron-ethyl (25), etc. In relation to herbicide-resistant weeds by county and site of action top 10 counties are the United States, Australia, Canada, France, Brazil, China, Spain, Israel, Japan and Germany [7] (**Table 1**).

In Serbia, study of weed resistance to herbicides started in the 1990s with resistance of *Amaranthus retroflexus* and *Chenopodium hybridum* to PS II inhibitors (atrazine) [8–10]. Until today, in Serbia, as a small county with less than 3 million ha arable lands, in the last 15 years, eight herbicide-resistant weed species were confirmed: *A. retroflexus*, *Setaria viridis*, *C. hybridum* and *Abutilon theophrasti* to PS II inhibitors, as well as *A. retroflexus*, *E. crus-galli*, *Datura stramonium*, *Chenopodium*

Country	Total number of resistant weed species	Number of resistant weed species according to the site of action			
		ALS	ACC-ase	PS II	EPSPS
USA	156	51	15	26	16
Australia	84	25	12	7	13
Canada	64	25	4	12	5
France	48	16	6	22	2
Brazil	42	19	6	4	8
China	41	14	8	1	2
Spain	37	8	2	18	5
Israel	36	12	6	12	2
Japan	36	21	2	1	3
Germany	32	10	5	13	0

Table 1. Top 10 countries with the most number of confirmed resistant weed species.

album and *Sorghum halepense* to ALS inhibitors [11–19]. According to the herbicide resistance mechanisms, all processes can be grouped as follows: target-site resistance, non-target-site resistance, cross-resistance and multiple-resistance [20–22].

Target-site resistance (TSR) is generally due to a single or several mutations in the gene encoding the herbicide-target enzyme, which, in turn, decreases the affinity for herbicide binding to that enzyme. Most, but not all cases of resistance to herbicide ALS inhibitors, ACC-ase, triazine, dinitroaniline etc. are due to modifications of the site of action of the herbicide. In addition, gene overproduction (amplification) is the most recently identified herbicide resistance mechanism, for example, EPSPS gene amplification correlates with glyphosate resistance in *Amaranthus palmeri* and *Kochia scoparia* [23–25], and causes resistance by increasing the production of the target enzyme, effectively diluting the herbicide in relation to the target site (**Figure 1**).

Non-target-site resistance **(NTSR)** is caused by mechanisms that reduce the amount of herbicidal active compound before it can attack the plant. Reduced absorption (penetration) or altered translocation, increased herbicide sequestration or enhanced herbicide metabolism (detoxification) can cause resistance due to the restriction of herbicide movement where the herbicide does not reach its site of action in sufficient concentration to cause plant mortality. Active vacuolar or cell walls sequestration can keep the herbicide from the site of action leading to resistance. For example, vacuolar herbicide sequestration correlates with glyphosate resistance in *Conyza canadensis*, *Lolium* sp. etc. [26, 27] (**Figure 1**). Finally, the biochemical reactions that detoxify herbicides can be grouped into four major categories: oxidation, reduction, hydrolysis and conjugation [28].

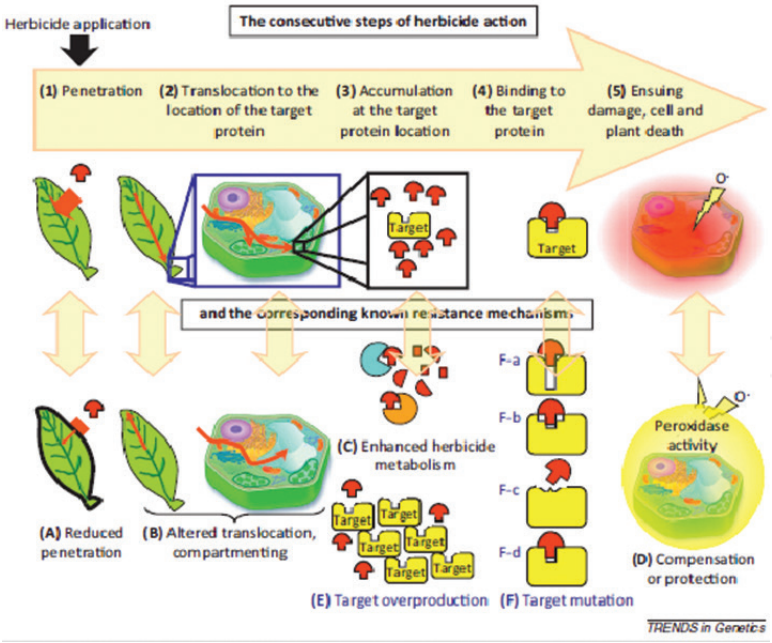

Figure 1. The route of the herbicide after the application, and the possible mechanisms of resistance in plant. After application: (1) herbicide absorption/penetration, (2) translocation, (3) accumulate at the target protein location, and (4) binding to the target protein, (5) disruption of the biosynthesis pathways or cell structures, and/or generation of cytotoxic molecules. NTSR mechanisms: (A) reduction in herbicide penetration, (B) altered translocation of the herbicide away from the target protein, (C) enhanced detoxification of the herbicide, or (D) enhanced neutralization of cytotoxic molecules generated by herbicide action. TSR mechanisms: (E) target protein overproduction, and/or (F) structural mutations that modify the 3D structure and electrochemical properties of the target protein. Structural mutations can have no, moderate or strong negative effects on the stability of herbicide binding to the target protein, which results in (F-a) no, (F-b) moderate or (F-c) marked reduction in herbicide sensitivity at the protein level, respectively; or can (F-d) increase the stability of herbicide binding to the target protein, which results in an increase in herbicide sensitivity at the protein level (downloaded from Ref. [32]).

Cross-resistance **(CR)** means that a single-resistance mechanism causes resistance to several herbicides. CR can be conferred by a single gene or by two or more genes influencing a single mechanism. There are two types of CR: target-site cross-resistance (TS-CR) and non-target-site cross-resistance (NTS-CR). The most common type of CR is TS-CR where an altered target site confers resistance to many or all of the herbicides that inhibit the same enzyme, for example, Trp-574-Leu amino acid substitution within the ALS gene was found in two populations of *Cyperus iria* after exposition to bispyribac-sodium, halosulfuron, imazamox and penoxsulam [29]. On the other hand, NTS-CR is type of herbicide resistance in which a mechanism other than resistant enzyme target sites is involved (e.g. reduced absorption, translocation, or enhanced herbicide detoxification) [30].

Multiple-resistance is a situation where two or more resistance mechanisms are present within the same plant, often due to sequential selection by herbicides with different modes of action (e.g. resistance of *Lolium* sp. populations to glyphosate and ACC-ase inhibitors, as well as resistance to glyphosate and ALS inhibitors were confirmed by multiple-resistance [31]).

2. Weed resistance to herbicides photosystem II inhibitors, triazines

The triazine herbicides were discovered in the J.R. Geigy Ltd. laboratories, an international chemical company founded in 1952 and based in Basel, Switzerland [33]. Generally, in the latter half of the twentieth century, triazines have played a significant role in the promotion of the crop production. Atrazine is one of the most used triazine herbicides in agriculture for control of annual monocots (*Setaria* sp., *E. crus-galli*, *Digitaria sanguinalis*) and dicot weed species (*Amaranthus* sp., *Chenopodium* sp., *Cirsium arvense*, *D. stramonium*, *Sonchus* sp., *Xanthium strumarium*, etc.) and is the most widely used herbicide in maize, orchards and sorghum crops. Triazines specifically inhibit photosystem II (PS II) in plants and in all organisms with oxygen-evolving photosystems. Generally, they prevent electron transfer by displacing plastoquinone (Q_B) from a specific binding site on the D1 protein subunit of PS II [34, 35].

The intensive use of triazines resulted in two important cases: appearance of atrazine-resistant weed species, leading to the increased use of herbicide mixtures or alternative herbicides. The first confirmed atrazine-resistant weed species [6] helped identify the herbicide-binding D1 protein in PS II. After the psbA gene was found and sequenced [36], the psbA gene from an atrazine-tolerant *Amaranthus* was then sequenced [37]. Based on their findings, the resistance is due to a chloroplast genome mutation of the psbA gene, which codes the D1 protein. The molecular analysis showed that resistance is due to the substitution of serine 264 to glycine (Ser-264-Gly) in many weed species [38–42]. The substituted urea herbicides, as PS II inhibitors [43] also bind in a niche on the D1 protein, but not at the identical site as the triazines.

A schematic diagram of the folding of the herbicide-binding site on the D1 protein [44], updated with further amino acids in triazine resistance, is given in **Figure 2** [45]. From total of 345 amino acids in the D1 protein, around 60 are part of the herbicide and Q_B-binding site. Arrows indicate possible mutations (such as Val-219, Ala-251, Phe-255, Gly-256, Ser-264

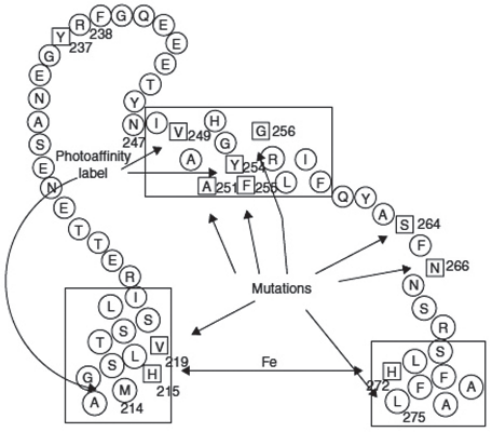

Figure 2. The amino acid sequence of the herbicide-binding D1 protein in the PS II. This work of Michel and Deisenhofer was honoured with the Nobel Prize. (downloaded from Ref. [45]).

Herbicide groups according the site of action	Number of weed species					Total
	1970–1979	1980–1989	1990–1999	2000–2009	2010–2016	
Inhibitors PS II (C1/5)	20	32	11	7	4	74
Inhibitors PS II (C2/7)	1	6	13	4	4	28
Inhibitors PS II (C3/6)	/	/	1	3	/	4
Inhibitors ESPSP enzyme	/	/	2	18	16	36
Inhibitors AHAS enzyme	/	11	62	53	33	159
Inhibitors ACC-ase	/	5	21	14	8	48
Total	21	54	110	99	65	

Table 2. The first confirmed cases of weed species that have developed resistance to different herbicides site of action according to decades.

and Leu-275) in herbicide-resistant plants and algae or amino acids tagged by herbicides azidoderivatives (Met-214 by azidoatrazine) [45].

Currently, resistance to herbicides that target photosynthesis at PS II has been documented in 74 weed species for triazines (C1/5 group), 28 in C2/7 and only 4 in C3/6 according to the data in the **Table 2** [7]. Except the usual amino acid substitution Ser-264-Gly in the D1 protein, reduced absorption, translocation and/or detoxification have been reported very often for resistance to triazines in many weed species (**Table 3**).

However, diverse chemical groups of herbicides PS II inhibitors (according to HRAC: C1—triazineas, triazinones, triazolinone, pyridazinones, phenyl-carbametes, uracils; C2—amides, ureas; C3—benzothiadiazinones, nitriles, phenyl pyridazines) bind to overlapping, but not identical sites on the D1 protein [43]. Several different amino acid substitutions that confer resistance to herbicide PS II inhibitors have been identified in or near the Q_B-binding niche such as: Ser-264-Thr in *Portulaca oleracea* [71], Ser-264-Gly and Val-219-Ile in *P. annua* and *K. scoparia* [64, 68, 70], Asn-266-Thr in *S. vulgaris* [73] as well as Ser-264-Gly, Ala-251-Val and Leu-218-Val in *C. album* [41, 59]. In addition, dependence of herbicides, interaction between herbicides, specific amino acid substitution, varying levels of cross or negative cross-resistance have been reported for different mutations in the D1 protein [64]. Resistance ratios for *P. oleracea* a Ser-264-Thr mutant were 8 and >6 for linuron and diuron, respectively; >800 for atrazine; and >20 for terbacil. Linuron resistant *P. oleracea* was negatively cross-resistant to pyridate and bentazon (0.75 and 0.5, respectively) [71].

Weed species	Mechanisms	
	Amino acid substitution	**Other mechanisms of resistance**
Abutilon theophrasti Medic.		Detoxification [45–49]
Alopecurus myosuroides Huds.		Detoxification [50–52]
Amaranthus tuberculatus Moq. Sauer.		Detoxification [53, 54]
Amaranthus retroflexus L.		Detoxification [55]
Amaranthus hybridus L.	Ser-264-Gly [37]	
Amaranthus powellii S. Wats.		Detoxification [56]
Bromus tectorum L.		Detoxification [57]
Brassica napus L.	Ser-264-Gly [58]	
Chenopodium album L.	Ser-264-Gly, Ala-251-Val, Leu-218-Val [41, 59]	Detoxification [55, 56, 60, 61]
Echinochloa crus-galli (L.) P. Beauv.		Reduced absorption and translocation, detoxification [60, 62, 63]
Kochia scoparia (L.) Schr.	Val-219-Ile [64]	
Lolium rigidum Gaudin.		Detoxification [65–67]
Poa annua L.	Ser-264-Gly, Val-219-Ile [40, 68–70]	
Portulaca oleracea L.	Ser-264-Thr [71]	
Solanum nigrum L.	Ser-264-Gly [72]	
Senecio vulgaris L.	Asn-266-Thr [73]	
Vulpia bromoides (L.) S.F.Gray.	Ser-264-Gly [42]	

Table 3. Confirmed mechanisms of resistance to herbicide PS II inhibitors in some weed species.

3. Weed resistance to herbicide ALS inhibitors

Herbicide inhibitors of acetoacetate synthase (ALS) and acetohydroxyacid synthase (AHAS) belong to several chemical classes: sulfonylurea (SU), triazolopyrimidines (TPs), pyrimidinyl(thio) benzoates, sulfonylaminocarbonyltriazolinones, imidazolinones (IMIs). The first commercial SU herbicide was chlorsulfuron, which was introduced by DuPont in 1982 for weed control in small grain crops. The SUs are highly active herbicides, effective at use rates as low as 2 g a.i. ha^{-1} [74]. Almost simultaneously, researchers at American Cyanamid discovered a structurally distinct family of herbicides, the IMIs, which were also shown to inhibit the ALS enzyme [75]. Since then, three additional chemical classes of ALS inhibitors have been discovered. Those products provide both pre-emergent and post-emergent control of many serious monocot and dicot weed species in many crops.

ALS is the first enzyme in the branched-chain amino acid pathway, which catalyzes the first steps in amino acid biosynthesis such as valine, leucine and isoleucine [76]. The first

case of resistance to ALS inhibitors (chlorsulfuron) was reported within 5 years after the introduction of SU herbicides, in 1987 in the United States [77]. Herbicide-resistant weed evolution is more common for ALS inhibitors compared to herbicides of other groups. Currently, 159 weed species have evolved resistance to ALS-inhibiting herbicides [7] according to decades that could be seen in **Table 2**. Weed resistance to ALS inhibitors is due to an alteration of the gene encoding the ALS enzyme. The positions in ALS from various sources (plant, yeast, bacteria) where mutations are known to confer resistance to one or more herbicides distributed across the α, β and γ domain of the protein (**Figure 3**) [78]. Weed species or genera with high incidence of target-site ALS resistance include *Amaranthus* spp., *K. scoparia* and *Papaver rhoeas*, among others. Studies have shown that mutations of eight amino acid residues are known to be involved in causing weed resistance: Ala-122, Pro-197, Ala-205, Asp-376, Arg-377, Trp-574, Ser-653 and Gly-654 (**Table 4**).

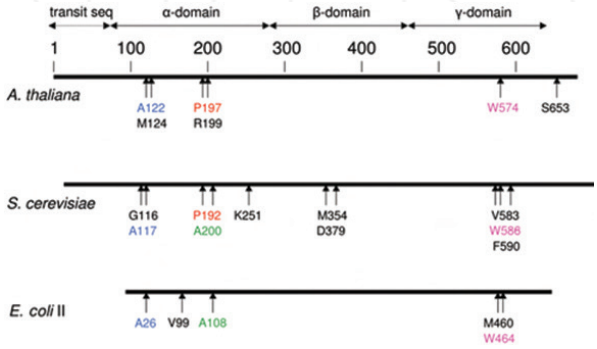

Figure 3. ALS mutations conferring herbicide resistance. Arrows point to positions in the sequences of ALS from different sources (plant, yeast, bacteria) where spontaneous or induced mutations result in an herbicide-insensitive enzyme. Colours designate substitutions occurring in more than one species (downloaded from Ref. [78]).

Weed species	Mechanism of resistance	
	Amino acid substitutions	**Other mechanisms of resistance**
Amaranthus retroflexus L.	Ala-122-Thr, Pro-197-Leu, Ala-205-Val, Asp-376-Glu, Arg-377-His, Trp-574-Leu, Ser-653-Thr [80]	
Amaranthus powellii S. Warts.	Ala-122-Thr, Asp-376-Glu, Arg-377-His, Ser-653-Thr	
Amaranthus hybridus L.	Ala-122-Thr, Asp-376-Glu, Arg-377-His, Ser-653-Asn	Detoxification [86]
Amaranthus blitoides S. Wats	Pro-197-Ser, Arg-377-His	
Amaranthus tuberculatus (Moq.) Sauer	Arg-377-His, Ser-653-Asn/Thr	Altered enzyme activity, detoxification [87, 88]
Amaranthus palmeri (S.) Warts.	Arg-377-His, Ser-653-Asn	Altered enzyme activity [87, 89]
Ambrosia artemisiifolia L.	Arg-377-His	

Weed species	Mechanism of resistance	
	Amino acid substitutions	**Other mechanisms of resistance**
Ambrosia trifida L.	Arg-377-His	Reduced translocation, detoxification, sequestration [90]
Alopecurus aequalis Sobol.	Pro-197-Thr, Arg-377-His	
Alopecurus myosuroides Huds.	Pro-197-Thr, Arg-377-His	
Anthemis cotula L.	Pro-197-Ser/Thr/Leu/Gln	
Apera spica-venti (L.) P.B.	Ala-122-Val, Pro-197-Ser/Thr/Ala/Asn, Arg-377-His, Trp-574-Leu/Met	
Avena fatua L.	Ser-653-Asn/Thr	
Bromus tectorum L.	Pro-197-Ser	
Capsella bursa-pastoris (L.) Med.	Pro-197-Ser/Thr/Leu/His	
Camelina microcarpa Andrz.	Arg-377-His	
Conyza canadensis (L.) Cronq.	Pro-197-Ser/Ala, Ala-205-Val, Asp-376-Glu, Trp-574-Leu	
Cyperus difformis L.	Pro-197-Ser/Ala/His	
Cyperus iria L., *C. escculentus* L.	Trp-574-Leu	
Descurainia sophia (L.) Webb.	Pro-197-Ser/Thr/Leu/Ala/His/Tyr, Asp-376-Glu, Arg-377-Leu	
Echinochloa crus-galli L.	Ala-122-Thr/Val, Arg-377-His	Detoxification [91]
Echinochloa phyllopogon (Stapf) Koss	Arg-377-His	Detoxification [92]
Galium aparine L.	Trp-574-Gly	
Galium spurium L.	Asp-375-Glu, Trp-574-Leu, Ser-653-Asn	
Helianthus annuus L.	Pro-197-Leu, Ala-205-Val	Altered enzyme activity [90]
Kochia scoparia (L.) Schrad.	Pro-197-Ser/Thr/Leu/Ala/Gln/Arg, Asp-376-Glu, Trp-574-Leu	Altered enzyme activity [93]
Lactuca serriola L.	Pro-197-Thr/His	
Lamium amplexicaule L.	Pro-197-Arg	
Lolium perenne L.	Asp-376-Glu	
Lolium rigidum Gaud.	Pro-197-Ser/Leu/Ala/Gln/Arg, Trp-574-Leu	Detoxification altered enzyme activity [94, 95]
Myosoton aquaticum (L.) Moench.	Pro-197-Ser/Glu	Detoxification [96]
Papaver rhoeas L.	Pro-197-Ser/Thr/Leu/Ala/His/Arg, Trp-574-Leu	
Poa annua L.	Ala-205-Phe, Trp-574-Leu	
Polygonum convolvulus L.	Trp-574-Leu	
Raphanus raphanistrum L.	Ala-122-Try, Pro-197-Ser/Thr/Ala/His, Asp-376-Glu, Trp-574-Leu	
Schoenoplectus juncoides Roxb.	Pro-197-Ser/Leu/His, Asp-376-Glu, Trp-574-Leu	

Weed species	Mechanism of resistance	
	Amino acid substitutions	**Other mechanisms of resistance**
Schoenoplectus mucronatus (L.) Palla	Pro-197-His, Trp-574-Leu	
Senecio vulgaris L.	Pro-197-Ser/Leu	
Setaria viridis (L.) Beauv.	Ser-653-Asn/Thr/Ile, Gly-654-Asp	Altered enzyme activity [97]
Sinapis arvensis L.	Pro-197-Ser, Asp-376-Glu, Trp-574-Leu	
Sisymbrium orientale Torn.	Pro-197-Ile, Trp-574-Leu	
Solanum ptycanthum Dunn	Ala-122-Thr, Ala-205-Val	
Sonchus asper (L.) Mill.	Pro-197-Leu	
Sorghum bicolor (L.) Moench		Altered enzyme activity [98, 99]
Sorghum halepense (L.) Pers.	Trp-574-Leu [100]	
Stellaria media (L.) Vill.	Pro-197-Gln, Trp-574-Leu	Altered enzyme activity [101]
Thlaspi arvense L.	Pro-197-Leu	
Xanthium strumarium L.	Ala-122-Thr, Ala-205-Val, Trp-574-Leu	Altered enzyme activity [102]

Amino acid substitution in weed-resistant species to ALS inhibitors downloaded from HRAC [103].

Table 4. Confirmed mechanisms of resistance to herbicide ALS inhibitors in some weed species.

The most different amino acid substitutions in α-domain at position Pro-197 have been linked in confirmed weed-resistant species such as: *K. scoparia* (Pro-197-Ser/Thr/Leu/Ala/Gln/Arg), *Descurainia sophia* (Pro-197-Ser/Thr/Leu/Ala/His/Tyr), *P. rhoeas* (Pro-197-Ser/Thr/Leu/Ala/His/Arg), *L. rigidum* (Pro-197-Ser/Leu/Ala/Gln/Arg), *Apera spica-venti* (Pro-197-Ser/Thr/Ala/Asn), etc. Also, the substitution of Trp-574-Leu confers resistance to several weed species (*A. retroflexus*, *C. iria*, *D. sophia*, *C. canadensis*, *K. scoparia*, *P. annua* etc.) and the levels of resistance are all high against SUs, IMIs and TPs (cross-resistance) [29, 79–83]. Generally, the low number of confirmed weeds resistant to ALS inhibitors is due to altered enzyme activity, reduced translocation and detoxification. Additionally, many weed populations resistant to ALS inhibitors have developed multiple-resistance to other chemical classes with different modes of action (e.g. auxinic herbicides, EPSPS inhibitors, ACC-ase inhibitors) [31, 84, 85].

4. Weed resistance to herbicides ACC-ase inhibitors

Herbicides acetyl-CoenzymeA carboxylase (ACC-ase) inhibitors are aryloxyphenoxy-propionates (APPs/FOPs), cyclohexanediones (CHDs/DIMs) and phenylpyrazoline. The first herbicide ACC-ase inhibitors commercialized in 1975 [104]. They are used as foliar

herbicides to control monocot weed species in dicot crops and some of them even in cereals or in rice. The mode of action of these herbicides is inhibition of fatty acid biosynthesis through blocking of the acetyl-CoenzymeA carboxylase [105]. Inhibition of lipid biosynthesis can explain the reduction of growth, increase in permeability of membrane and the ultrastructural effects commonly observed. In living organisms, ACC-ase exists in two different types: multi-subunit type and multi-functional type with 17–51 kDa (prokaryote) and 220–280 kDa (eukaryote) in size, respectively [106]. In dicot plants, the enzyme is structurally distinguished from the enzyme of monocots which contains four regions (biotin carboxylase, biotin carboxy carrier protein, carboxyl-transferase α and β), while in dicots, they are encoded on separate proteins.

The frequent use of FOPs and DIMs has resulted in the development of resistance to ACC-ase inhibitors in some monocot species in many countries in the world. Currently, 48 weed species have evolved resistance to these herbicides [7]. By decades, dynamics of the confirmation of the first cases of resistant weed species to the ACC-ase can be seen in **Table 2**. Generally, mechanisms of resistance to ACC-inhibiting herbicides can be divided in two categories: ACC-related and metabolism-based. Target-site resistance to ACC-ase inhibitors due to the herbicides binding to the carboxyl-transferase region within the ACC-ase enzyme results in amino acid substitution in that region (**Figure 4**) [107, 108]. Weed species or genera with high affinity of target-site ACC-ase resistance are *A. myosuroides*, *Avena* sp., *Bechmannia syzigachne*, *E. crus-galli*, *Lolium* sp., etc. Most commonly amino acid substitution such as Ile-1781-Leu, Trp-1999-Cys, Trp-2027-Cys, Ile-2041-Asn, Asp-2078-Gly, Cys-2088-Arg, Gly-2096-Ser was confirmed in monocot resistant populations of weed species [109–116]. Amino acid substitutions such as Asp-2078-Gly and Cys-2088-Arg usually provide strong level of resistance to all ACC-ase (FOPs, DIMs, pinoxaden) inhibitors [81]. Moreover, altered enzyme activity, gene expression and detoxification were very often included in weed resistance to ACC-ase inhibiting herbicides (**Table 5**). Also, in some population of weed species such as *A. myosuroides* [117], *E. crus-galli* [118], *L. rigidum* [111] and *Lolium perenne* [85], target and non-target multiple-resistance, which involves ACC-ase and ALS inhibitors or ACC-ase and EPSPS inhibitors, was confirmed.

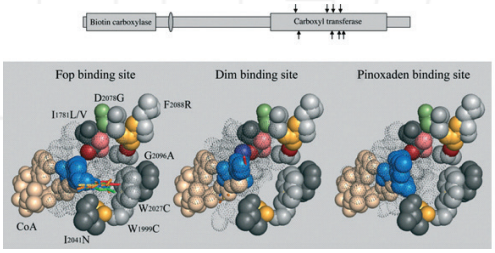

Figure 4. Single amino acid mutations in acetyl-CoA carboxylase in monocot-resistant weed populations (downloaded from Ref. [108]).

Weed species	Mechanism of resistance	
	Amino acid substitutions	**Other mechanisms of resistance**
Alopecurus aequalis Sobol.	Ile-1781-Leu [119]	
Alopecurus myosuroides Huds.	Ile-1781-Leu, Trp-2027-Cys, Ile-2041-Asn, Asp-2078-Gly, Gly-2096-Ala [110, 112]	Detoxification, gene expression [120–122]
Avena fatua L.	Ile-1781-Leu, Trp-1999-Cys,Trp-2027-Cys, Ile-2041-Asn, Asp-2078-Gly, Cys-2088-Arg, Gly-2096-Ser [109, 114]	Detoxification [123, 124]
Avena sterilis L.	Ile-1781-Leu, Trp-1999-Cys, Trp-2027-Cys, Ile-2041-Asn, Asp-2078-Gly, Cys-2088-Arg [115]	Detoxification [123, 125]
Bechmannia syzigachne (Steud.) Fernald	Ile-1781-Leu, Ile-2041-Asn, Asp-2078-Gly [126, 127]	
Echinochloa crus-galli (L.) Beauv.	Ile-1781-Leu [128]	Altered enzyme activity, gene expression [129]
Echinochloa colona (L.) Link.		altered enzyme activity [130]
Eleusine indica (L.) Gaertn	Asp-2078-Gly, Thr-1805-Ser [131]	
Hordeum glaucum (Steud.) Tzvelev	Ile-1781-Leu, Gly-2096-Ala [132]	
Hordeum leporinum (Link) Arcang.	Ile-1781-Leu, Gly-2096-Ala [132]	Detoxification, altered enzyme activity [133]
Lolium multiflorum Lam.	Ile-1781-Leu (Ile-418-Leu), Cys-2088-Arg [134, 135]	Detoxification [136]
Lolium perenne L. ssp. *multiflorum* Lam.	Ile-1781-Leu, Trp-2027-Cys, Ile-2041-Asn, Asp-2078-Gly [137, 138]	
Lolium rigidum Gaud.	Ile-1781-Leu, Ile-2041-Asn, Asp-2078-Gly, Cys-2088-Arg, Gly-2096-Ala, Trp-2027-Cys [111, 116]	Detoxification [139, 140]
Lolium sp.	Ile-1781-Leu, Trp-1999-Cys, Ile-2041-Asn/Val, Asp-2078-Gly, Cys-2088-Arg, Gly-2096-Ala [113]	
Pseudosclerochloa kengiana	Trp-1999-Ser [141]	
Setaria viridis L. Beauv.	Ile-1780-Leu [142]	Altered enzyme activity [143]
Sorghum halepense (L.) Pers.	Ile-2041-Asn [144]	Altered enzyme activity [145]

Table 5. Confirmed mechanisms of resistance to herbicide ACC-ase inhibitors in some weed species.

5. Weed resistance to herbicide EPSPS inhibitors, glyphosate

Glyphosate was discovered and developed as a non-selective herbicide by Chemical Company Monsanto in 1974. N-(phosphonometil) glycine, the active ingredient in glyphosate, is a derivate of the amino acid glycine and phosphonic acid. It's mode of action in relation to the enzyme EPSPS (5-enolpyruvylshikimate-3-phosphate synthase) preventing the biosynthesis

of the aromatic amino acids required for the production of growth regulators, anthocyanins, phenolics and proteins [146]. The site of action is located in the chloroplast and it was confirmed 8 years after glyphosate introduction [146]. Broad weed spectrum (annual and perennial, monocots and dicots), high efficacy, lack of soil activity and low mammalian toxicity are key characteristics that make glyphosate the world's most widely used herbicide [147]. Because glyphosate is inherently non-selective, selectivity has often been achieved by placement and timing, for example, as a pre-plant or pre-emergence herbicide for the control of weeds in no-till systems and for turf-grass renovation [104]. The introduction of genetically modified glyphosate resistant crops in the United States and other parts of the world [148] has led to enormous increase of glyphosate use on arable land (cotton, canola, corn, wheat, sugar beets, potatoes, etc.) as a post-emergence herbicide.

Glyphosate-resistant weeds were not found during the first 15 years of glyphosate use (1972–1997). Based on the resistance risk criteria for assessing the risk of developing weed resistance to glyphosate, it was estimated that the glyphosate has low risk for the evolution of weed resistance [149]. However, in the last 19 years (1998–2016), glyphosate resistance in 36 weed species was confirmed and according to the decades, it looks like this: 2 (first decade), 18 (second) and 16 species (the last, third) (**Table 2**) [7]. Mechanism of glyphosate resistance to weed species includes target-site mutation, target-site gene amplification/expression, active vacuole sequestration, limited cellular uptake and a rapid necrosis response [21].

In a number of cases of confirmed weed resistance to glyphosate, the resistance was based on some different mechanisms which include non-target-site (limited absorption and translocation, vacuolar sequestration) and target-site resistance (amino acid substitution, ESPSP gene expression/amplification, altered enzyme activity) (**Table 6**). Generally, usually confirmed

Weed species	**Mechanisms**	
	Amino acid substitution	**Other mechanisms of resistance**
Amaranthus tuberculatus Moq. Sauer.	Pro-106-Ser [150, 151]	Gene expression [150, 151]
Amaranthus palmeri S. Wats.		Gene expression [23, 24, 152]
Abutilon theophrasti Medic.		Reduced absorption and translocation [153, 154]
Cirsium arvense (L.) Scop.		Reduced absorption and translocation [155]
Conyza canadensis (L.) Cronq.		Reduced absorption and translocation, detoxification, vacuole sequestration [26, 156–160]
Conyza bonariensis (L.) Cronq.		Reduced absorption and translocation [161]
Chenopodium album L.		Reduced absorption and translocation [162]
Cyperus esculentus L.		Reduced absorption and translocation [163]
Cyperus rotundus L.		Detoxification [164]
Eleusina indica (L.) Gaertn.	Pro-106-Ser/Thr [165–167]	

Weed species	Mechanisms	
	Amino acid substitution	Other mechanisms of resistance
Echinochloa colona (L.) Link.	Pro-106-Ser [168]	
Kochia scoparia (L.) Schr.		Detoxification, gene expression [25]
Lolium rigidum Gaudin.	Pro-106-Ser/Ala/Thr/Leu [169, 170]	Reduced absorption and translocation, altered enzyme activity [171–177]
Lolium multiflorum Lam.	Pro-106-Ser [178]	Reduced absorption and translocation [178, 179]
Lolium perenne L. ssp. *multiflorum* Lam.		Gene expression [180]
Poa annua L.	Pro-106-Ala [181]	Reduced translocation [181]
Sorghum halepense (L.) Pers.		Reduced absorption and translocation [182]

Table 6. Confirmed mechanisms of resistance to EPSPS inhibitor in some weed species.

cases of weed resistance to glyphosate were due to reduced absorption and translocation of the herbicide. Further, cDNA sequence analysis of the EPSPS gene indicated that resistance to glyphosate was based on substitution of proline with serine (Pro-106-Ser), alanine (Pro-106-Ala), threonine (Pro-106-Thr), or leucine (Pro-106-Leu)) at the position 106 of the EPSPS protein in many weed species (*Amaranthus tuberculatus*, *E. indica*, *E. colona*, *L. rigidum*, *Lolium multiflorum*, *P. annua*).

6. Management strategies for herbicide-resistant weeds

Strategy for herbicide-resistance weed management must involve all the available preventive, cultural, mechanical and chemical measures for effective, safe and cost-effective weed control [183]: (a) survey of present weed flora; (b) preventing weed seed production and reduction of weed seed in the soil seed-bank; (c) prevention of the movement of seeds and vegetative propagules from field to field or from field margins (or lost field) to field; (d) keep arable and non-arable land as weed free as possible; (e) sowing pure crop seeds; (f) growing competitive crops that can suppress weeds; (g) destruction of weed seeds in post-harvest materials (e.g. Integrated Harrington Seed Destructor); (h) use mechanical and physical measures where appropriate; (i) using herbicides with different modes of action, tank mixtures and sequential applications; (j) use of recommended herbicide rate for certain number of weed populations; (k) adopting crop rotations that allow use of herbicides of alternative mode of action; (l) intensify research and professional communication and grower education programs and (m) publish guidelines for managing anti-resistant strategy.

The state government sectors, universities and research institutes, technology development centres, farmers and other relevant stakeholders were called to proactively address emerging weed resistance problems and to develop cost-effective resistance-management strategy and practices that support effective weed control.

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