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Review

Herbicide Resistance in Weeds: Evolution, Global Expansion and Confirmed Cases in Serbia

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Abstract: Weed resistance to herbicides is one of the most serious challenges of modern crop production and has significant economic and environmental consequences. Since the first recorded cases in the middle of the last century, the number of resistant weed populations worldwide has been steadily increasing, especially in intensive agricultural systems based on long-term and repeated application of herbicides with the same mechanism of action. To date, hundreds of resistant weed populations to various groups herbicide have been confirmed, among which acetolactate synthetase (ALS), acetyl-Coa carboxylase (ACCase), photosystem II and 5-enolpyruvatshikimate-3-phosphate synthetase (EPSPS) inhibitors dominate. This paper presents an overview of the development, mechanisms and prevalence of weed resistance to herbicides at the global level, with special emphasis on the situation in Serbia. Confirmed cases of resistance in domestic agroecosystems were analyzed, especially in economically important weed species such as *Ambrosia artemisifolia, Sorghum halepense* and *Amaranthus retroflexus*. Special attention is paid to resistance to ALS inhibitors, as the most common group of herbicides with the largest number of registered resistant biotypes worldwide and Serbia. The paper higlight the need for systematic monitoring and the implementation of integrated and anti-resistance strategies in order to preserve herbicide efficacy and ensure sustainability agricultural production.

Keywords: *Herbicide resistance; acetolactate synthase (ALS) inhibitors; resistant weed biotypes; integrated weed management; Serbia.*

1. Introduction

Herbicides are the basis of modern weed control systems in intensive agricultural production due to their high efficiency and economic justification. However, continued reliance on herbicides, often based on a limited number of mechanisms of action, has led to strong selection pressure and accelerated development of resistant weed populations [18]. Weed resistance to herbicides is defined as the ability of individual plants within a population to survive the application of herbicides at doses lethal to susceptible biotypes of the same species [5,17]. This phenomenon results from genetic variability in weed populations, where long-term and repeated application herbicide favors the survival and spread of resistant individuals [6,19]. As a consequence, the effectiveness of chemical control decreases, while production costs and environmental risks increase [9,11]. Over the past decades, weed resistance has evolved into a global problem that threatening the sustainability of modern agriculture [9,12]. An increase in resistant biotypes has been recorded in numerous weed species and across almost all major herbicide groups, with ALS inhibitors being the most common [11,23]. The development of resistance is further encouraged by simplified crop rotation, monoculture dominance and reduced implementation of non-chemical control measures [3,17]. In recent years, Serbia has recorded an increase in confirmed cases of weed resistance, particularly in intensive crop production systems. Resistant biotypes have been identified in economically important species such as *Ambrosia artemisifolia, Sorghum halepense* and *Amaranthus retroflexus*, significantly complicates their control and threatening crop yield stability [22,27]. These trends indicate the need for systematic monitoring of resistance and adaptation of weed management strategies, with emphasis on integrated approaches [15].

2. Methodology of review work

This paper represents a review study based on the analysis and synthesis of domestic and international literature scientific related to herbicide resistance [8,21]. Literature was collected trought searches of relevant scientific databases, including Web of Science and Scopus, as well as specialized sources such as the Weed Science database and publications of the Herbicide Resistance Action Committee (HRAC) [13]. The review includes original research articles, review papers and expert reports addressing resistance mechanisms, historical development,global distribution of resistant biotypes and confirmed cases in Serbia and the region [11,12]. Special emphasis was placed on literature published in the last two decades, while earlier foundational studies were also considered to better understand the evolution of resistance [10,20]. Data on the number and distribution of resistant biotypes were obtained from international surveys and databases [11,12] and analyzed using a descriptive method to identify dominant resistance mechanisms and assess the importance of integrated weed management strategies [3,17].

3. History of weed resistance to herbicides

The first documented cases of weed resistance to herbicides were recorded in the mid-20th century, shortly after the introduction of intensive chemical weed control [10,20]. Resistance was initially confirmed in species resistant to photosystem II inhibitors, where repeated of the same active substances led to rapid selection and emergence of resistant biotypes [20].

During the 1970s and 1980s, with the expansion of new herbicide groups, the number of resistant weed populations increased worldwide [11,12]. A particularly significant rise in resistance followed the introduction of herbicides with specific and highly effective mechanisms of action, such as ALS and ACCase inhibitors [19,23]. Although these herbicides enabled effective weed control at low doses, their repeated application created favorable conditions for rapid resistance evolution [6,19].

In the 1990s, resistance development intensified due to simplified production systems, reduced crop rotation and increased depedence on chemical control [1,9]. During this period, cases of cross- and multiple resistance were increasingly reported, where certain weed populations exhibited resistance to herbicides with different mechanisms of action [2,16]. These cases represented a serious challenge for weed management and revealed the limitation of purely chemical control strategies [3].

At the beginning of the 21st century, the widespread adoption of herbicide-tolerant crops has further influenced resistance dynamics. Intensive and long-term application of total herbicides, primarily glyphosate, led to resistance developtment in numerous weed species [1,16]. These cases confirmed that even herbicides initially considered low-risk resistance are not exempt from evolutionary adaptation [6,19]. Today, the continuous increase in resistant species and biotypes underscores the necessity of revising weed control strategies and implementing integrated systems combining chemical and non-chemical measures [3,17,27].

4. Mechanisms of weed resistance to herbicides

Herbicide resistance results from evolutionary processes within weed populations under prolonged and intense selection pressure caused by herbicide application [6,18,19]. Resistance mechanisms vary depending on species biology, herbicide mode of action production conditions.

The main mechanisms are classified as:

- Target-Site Resistance (TSR) [7,18,28]
- Non-Target-Site Resistance (NTSR) [6,18,25]
- Cross-Resistance (CR) [2,23]
- Multiple resistance (MRI) [2,16]

Target-site resistance involves molecular changes affecting herbicide binding to the target enzyme or protein. The most common from includes mutations in the gene encoding the target enzyme, leading to reduced or abolished herbicide inhibition [7,28]. This mechanisms is characteristic of herbicides with specific modes of action, such as ALS, ACCase and EPSPS inhibitors [19,23,28]. In addition to point mutations, increased expression of the target enzyme may also contribute to resistance development [18].

Non-target-site resistance includes mechanisms that reduce the concentration of active substance reaching the target site, such as reduced absorption, limited translocation or enhanced metabolic detoxification [6,18]. Metabolic resistance is particularly significant and involves enzyme systems such as cytochrome P450 monooxygenases, glutathione-S-transferases, and glycosyltransferases, which detoxify herbicides before they exert phytotoxic effect [6,25]. Unlike target site resistance, these mechanisms may confer resistance to multiple herbicide group [2,16].

5. Resistance of weeds to ALS inhibitors

Herbicides that inhibit the enzyme acetolactate synthetase are one of the most important and widely used groups of herbicides in modern agriculture. These herbicides work by blocking the synthesis of essential amino acids (valine, leucine, and isoleucine), which leads to a stunt in plant growth and development. Due to their high efficacy, wide spectrum of action and application in low doses, ALS inhibitors have quickly become the basis in weed control in various arable crops. However, it is precisely these traits that have contributed to their intensive application, which has resulted in reduced selection pressure and rapid development of resistance. Weed resistance to ALS inhibitors is now the most widespread form of herbicide resistance in the world, with the highest number of confirmed resistant species and biotypes compared to other mechanisms of action [9]. The most common mechanism of resistance to ALS inhibitors is resistance to the primary site of action, which occurs as a result of point mutations in the gene encoding the ALS enzyme [11]. These mutations lead to changes in the structure of the enzyme, thereby reducing or completely preventing the binding of the herbicide, while retaining the catalytic function of the enzyme. To date, a number of mutational positions have been identified that are associated with resistance to ALS inhibitors, with different mutations leading to varying degrees of cross-resistance within this group of herbicides. In addition to resistance at the primary site of action, resistance outside the primary site of action has also been confirmed in some weed species, most often in the form of increased metabolic degradation of herbicides. This type of resistance further complicates their control, as it can lead to reduced susceptibility to several chemically different ALS inhibitors, but also to herbicides with other mechanisms of action. In Serbia, weed resistance to ALS inhibitors has been confirmed in several of the most economically important species, which is a serious problem in the production of arable crops. Cases of resistance are particularly pronounced in *Ambrosia artemisiifolia*, where cross-resistance to several ALS inhibitors has been confirmed, as well as in other broadleaf and narrow-leaved weed species [14]. These examples point to the long-term and intensive use of herbicides from the same group, as well as the need to change existing weed control strategies. Due to the high risk of further development and spread of resistance, weed management with ALS inhibitors requires an integrated approach. The rotation of herbicides with different mechanisms of action, the application of different active substances as well as the inclusion of non-chemical control measures, are key elements in preserving the effectiveness of this important group of herbicides.

Resistance of weeds to other groups of herbicides

In addition to acetolactate synthetase (ALS) inhibitors, resistance has been confirmed to other groups of herbicides with different mechanisms of action. Although the number of resistant biotypes to these herbicides is smaller compared to ALS inhibitors, their importance in practice is extremely high, as it includes the most economically important weed species. Resistance to herbicides that inhibit acetyl-CoA carboxylase (ACCase) has been mainly observed in narrow-leaved weed species. This group of herbicides is used extensively in the control of grass weeds, which has led to the emergence of resistant populations in species such as *Avena fatua, Lolium rigidum* and *Sorghum halepense* [13,15,16]. The mechanisms of resistance to ACCase inhibitors most often involve mutations in the primary enzyme.

Resistance to photosystem II inhibitors (PSII), among which triazines are the most prevalent, is one of the earliest recorded forms of weed resistance to herbicides [19]. Although the use of these herbicides has decreased compared to previous decades, resistant biotypes are still present, especially in species such as *Chenopodium album* and *Amaranthus spp* [20,21]. These cases indicate the long-term persistence of resistant populations and the long-term consequences of intensive herbicide use.

In recent decades, special attention has been drawn to the resistance of weeds to inhibitors of 5-enolpyruvatshikimate-3-phosphate synthetase (EPSPS), i.e. glyphosate. The introduction of glyphosate-tolerant crops has led to its massive deployment, resulting in the emergence of resistant populations in a large number of weed species. Glyphosate resistance has been reported in species such as *Amaranthus palmer, Conyza canadensis,* and *Lolium spp.* [23,24]. In Serbia, resistance to these groups of herbicides is less prevalent compared to ALS inhibitors, but there are confirmed cases of reduced sensitivity of certain weed populations. These examples further confirm that weed resistance is not limited to a single group of herbicides, but is a complex and dynamic problem that requires a comprehensive approach to weed management.

6. Current state of weed resistance

Weed resistance to herbicides is now a global problem that affects all regions of the world. According to the International Weed Resistance Database [9,25] led by the Herbicide Resistance Action Committee (HRAC), a total of 539 weed-resistant biotypes have been confirmed worldwide to various mechanisms of action of herbicides These data indicate a continuous increase in the number of resistant populations. The largest number of cases was recorded in intensive production systems dominated by long-term use of the same or related active substances. Globally, resistance to ALS inhibitors remains the most prevalent, with the highest number of confirmed resistant species. In addition, a significant number of cases relate to resistance to ACCase inhibitors and glyphosate, especially in regions with a high proportion of monocultures and widespread use of herbicides of tolerant crops. Multiple resistance, in which weed populations show resistance to multiple groups of herbicides, is becoming more common and poses a serious challenge to the sustainability of modern weed management systems.

The global distribution of herbicide-resistant weed biotzpes according to herbicide site of action is presented in Figure 1, highlighting the predominance of resistance to ALS inhibitors.

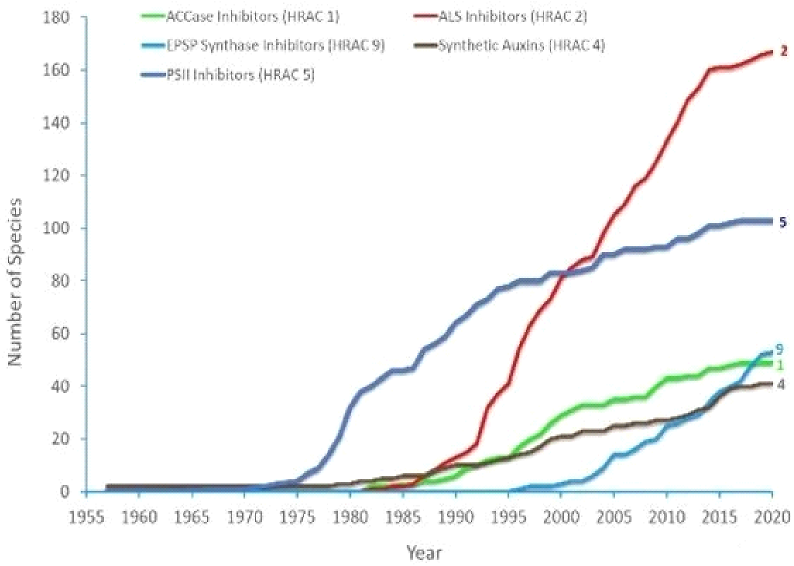

Figure1. Global distribution of herbicide-resistant weed biotypes by herbicide site of action. Data source: International Herbicide-Resistnt Weed Database (HRAC).

In recent years, cases of resistance have been confirmed in several economically important weed species in Serbia, which indicates the presence of the same trends that have been recorded at the global level. The most pronounced problems relate to resistance to ALS inhibitors, especially in broadleaf weed species in arable crops. Resistant biotypes *Ambrosia artemisifolia* is one of the most significant problems, given its wide distribution and confirmed cross-resistance to multiple ALS inhibitors. In addition to ragweed, cases of resistance to other weed species, including *Sorghum halepense* and *Amaranthus spp*, have also been registered in Serbia [14,22,26]. This makes it even more difficult to control different production systems. These cases are most often associated with long-term application of herbicides with the same mechanism of action, limited crop rotation, and insufficient application of integrated weed control measures. For a clearer overview of confirmed cases of resistance in Serbia, Table 1 shows the weed species in which resistance has been confirmed, the mechanisms of action of herbicides and the zear of first confirmation.

Table 1. Confirmed resistant weed species in Serbia, mechanisms of resistance and zear of first confirmation.

Type of weeds	The mechanism of resistance	Herbicide group	Year of confirmation
Ambrosia artemisiifolia	Mutation ALS	ALS inhibitors	2015
Sorghum halepense	Target site	ACCase inhibitors	2018
Amaranthus retroflexus	Metabolic	ALS inhibitors	2020

As shown in Table 1, the largest number of congirmed biotypes in Serbia is related to resistance to ALS inhibitors, which is in line with long-standing and widespread use in crop production. Although the number of confirmed cases of resistance in Serbia is lower compared to some regions of the world, the presence of resistant populations is a seroius warning. These data indicate the need to establish systematic monitoring of weed resistance in Serbia, as well as the importance of adapting weed management stratedies in accordance with modern knowledge, in order to prevent further spread of resistant biotypes and preserve the effectiveness of existing herbicides.

7. Anti-resistant weed management strategy

Effective management of weed resistance requires the implementation of long-term and integrated strategies that go beyond relying solely on chemical control measures [3,17]. Past experience clearly indicates that the continued use of herbicides with the same mechanism of action is a major risk factor for the development of resistance [16,25], and that changes in weed control approaches are necessary to preserve effective existing herbicides [17,27]. One of the basic anti-resistance strategies is the rotation of herbicides with different mechanisms of action [3,17]. The application of herbicides from the same HRAC group each season significantly increases the risk of resistance, especially with herbicides such as ALS and ACCase inhibitors [16,25]. Therefore, the careful selection of active ingredients, while respecting the recommended doses and timing of application, is crucial for the long-term effectiveness of chemical weed control [17]. The use of herbicide mixtures with different mechanisms of action is an additional strategy for slowing down the development of resistance, provided that these active substances are effective aggaints the target weed species [3,17]. This approach reduces the likelihood of survival of resistant individuals and contributes to more effective weed control [16], but requires careful selection of combinations to avoid negative effects on the crop and the environment. In addition to chemical measures, non-chemical methods play a key role in integrated weed management [3,27]. Crop rotation, mechanical measures, adjustment of sowing time and crop density, as well as the use of cover crops, can reduce the weed seed bank in the soil and thereby decrease herbicide reliance [17,27]. This is especially important in regions where weed resistance has already been confirmed [26].

Monitoring and early detection of resistance represent an important element of anti-resistance strategies [5,12]. Observing reduced herbicide effectiveness and confirming resistance through biological and molecular methods allows for rapid adaptation of control strategies and prevents further spread of resistant populations [6,7]. Resistance monitoring is therefore of particular importance for sustainable agricultural systems.

8. Conclusions

Weed resistance to herbicides is one of the most serious challenges of modern agriculture, with long-term consequences for production efficiency. The continuous increase in the number of resistant weed biotypes globally confirms that resistance is not a transient problem, but an evolutionary response of weeds to intense selection pressure caused by long-term application of herbicides. According to the international resistance databases, 539 resistant weed biotypes have been confirmed worldwide to date, with resistance to ALS inhibitors being the most common. These data indicate a high risk associated with the prolonged use of herbicides with same mechanisms of action and reliance exclusively on chemical weed control.

In Serbia, cases of resistance have been confirmed in significant weed species, among which *Ambrosia artemisiifolia* stands out with confirmed cross-resistance to ALS inhibitors. Resistance has also been recorded in *Sorghum halepense* and *Amaranthus spp.*

The presented overview highlights the need to implement integrated and long-term sustainable weed management strategies, including rational herbicide use, rotation of mechanisms of action, and the introduction of non-chemical control measures. Of particular importance is the establishment of systematic resistance monitoring and the strengthening of cooperation between scientific institutions, advisory services and agricultural practice. Only through a responsible and coordinated approach is it possible to slow down the further development and spread of weed resistance, preserve the effectiveness of existing herbicides, and ensure the sustainability of crop production, both in Serbia and globally.

Conflicts of Interest: The authors declare no conflicts of interest.

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