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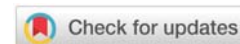
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## Review Article

# Impacts of climate change on crop-weed dynamics: Challenges and strategies for weed management in a changing climate

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## Abstract

Rising carbon dioxide (CO<sub>2</sub>) concentrations, global temperature variations, and precipitation changes are key factors influencing future weed dynamics and agricultural productivity. Weeds, having diverse gene pools and physiological plasticity, are likely to exhibit greater resilience and adaptability to changes in CO<sub>2</sub> concentrations and temperature, potentially outcompeting crops. The global increase in carbon dioxide emissions by 51% is of concern, given that CO<sub>2</sub> accounts for three-fourths of total emissions. Weeds with C<sub>3</sub> and C<sub>4</sub> photosynthetic pathways may display distinct responses to elevated CO<sub>2</sub> and temperature, impacting the dynamics of crop-weed competition. Furthermore, climate change can influence the efficacy of herbicides, further complicating weed management. Understanding and assessing the changes in climatic factors and their interactions at the crop-weed interface is crucial for developing effective weed management strategies in a changing climate. While the positive response of C<sub>3</sub> crops to increased CO<sub>2</sub> may reduce the competitiveness of certain C<sub>4</sub> weeds, the potential emergence of C<sub>3</sub> weeds in C<sub>4</sub> or C<sub>3</sub> crops, particularly in tropical regions, poses a significant concern.

Therefore, comprehensive research is needed to formulate adaptive weed management approaches that consider the multifaceted impacts of climate change on crop-weed interactions. This paper emphasizes the urgency of addressing the impact of climate change on weed growth and its implications for weed management in order to ensure sustainable crop production in a changing climate.

## Introduction

The impact of climate change on food security is significant, affecting both crops and weeds directly and indirectly. Changes in global temperature, precipitation, and rising carbon dioxide (CO<sub>2</sub>) concentrations pose challenges for weed management and crop production. Weeds possess a diverse gene pool and greater physiological plasticity, allowing them to exhibit resilience and adapt better to changing CO<sub>2</sub> levels and higher temperatures, often outcompeting crops. Among various agricultural pests, weeds cause the most substantial yield loss (34%), surpassing insect pests (18%) and diseases (16%). Weeds with C<sub>3</sub> and C<sub>4</sub> photosynthetic pathways might exhibit distinct responses to increased CO<sub>2</sub> levels and temperatures, thereby modifying the dynamics of competition between crops and weeds. In South

Asia, weed competition has resulted in significant yield losses of 183 kg/ha in rice and up to 88 kg/ha in wheat [1].

The economic implications of weeds are staggering, with an estimated loss of approximately 10 billion USD in India alone across ten major crops. These crops include groundnut (35.8%), pearl millet (27.6%), soybean (31.4%), maize (25.3%), sorghum (25.1%), green gram (30.8%), sesame (23.7%), mustard (21.4%), wheat (18.6%), transplanted rice (13.8%) DSR (21.4%), [2], and vegetable peas (46.82%) [3]. These findings underscore the significant economic burden imposed by weeds on agricultural production and highlight the urgency of effective weed management strategies under changing climate scenarios.

Two major factors responsible for climate change are

the rise in global temperature and increased emission of greenhouse gases (CH<sub>4</sub>, N<sub>2</sub>O, CO<sub>2</sub>, CFC, etc.). In this paper, we are focussing on CO<sub>2</sub> as it has a major impact on crops and weeds, and the various adaptive mechanisms by which plants adapt and evolve to survive and flourish in changing climatic conditions.

### Rise in global temperature

The global temperature has been reliably measured since 1880, and during the period from 1880 to 1940, the average annual temperature experienced a 0.2°C increase. Subsequently, between 1940 and 1970, the temperature remained stable without significant fluctuations (Figure 1). However, starting from 1970, a trend of temperature rise has emerged, with each subsequent decade experiencing an increase of 0.18 °C. Overall, compared to the baseline temperature, the average worldwide temperature has risen by 0.9 °C.

According to the data obtained from Rhodium Group, on a global scale, greenhouse gas emissions increased by 53% between 1990 and 2019. Although there was a temporary decline in the average global CO<sub>2</sub> emissions in 2020, the trend was not sustained. Preliminary numbers found that CO<sub>2</sub> emissions increased again in 2021. Throughout the period from 1990 to 2015, there was a global rise in emissions for all major greenhouse gases, as depicted in Figure 2. Specifically, there was a 51% rise in net CO<sub>2</sub> emissions, which is particularly noteworthy since CO<sub>2</sub> accounts for approximately 75% of the total global emissions. Methane emissions showed the smallest increase, amounting to 17%, while nitrous oxide emissions saw a growth of 24%. The emissions of fluorinated gases more than tripled during this period [6].

The impact of climate change on crop production depends on the specific factors of climate variability (Table 1). For example, increased CO<sub>2</sub> levels can be advantageous for certain crops (such as C<sub>3</sub> crops like rice, wheat, barley, soybean, and cotton). However, the positive effects of any single climate change factor can only be realized if other growth conditions for the crops are optimal. The positive effects of increased CO<sub>2</sub> on most crops are offset by higher temperatures, with no benefits observed for C<sub>3</sub> crops (such as beans and groundnuts)

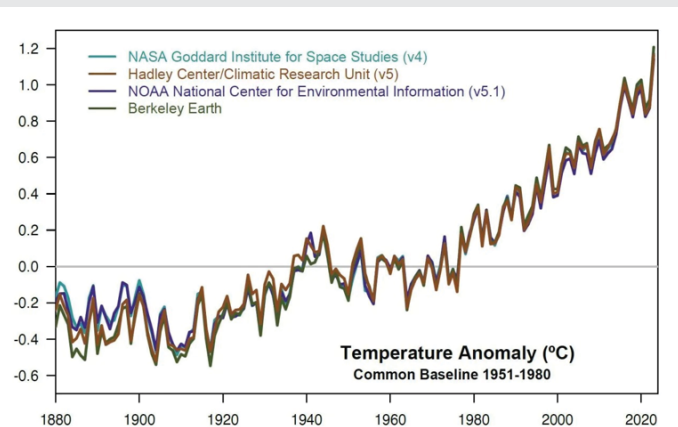


Figure 1: Rise in global temperature (<https://science.nasa.gov/climate-change/scientific-consensus/>) [4].

Global GHG emissions for 1990-2020 and preliminary estimates for 2022  
Billion metric tons of CO<sub>2</sub>e

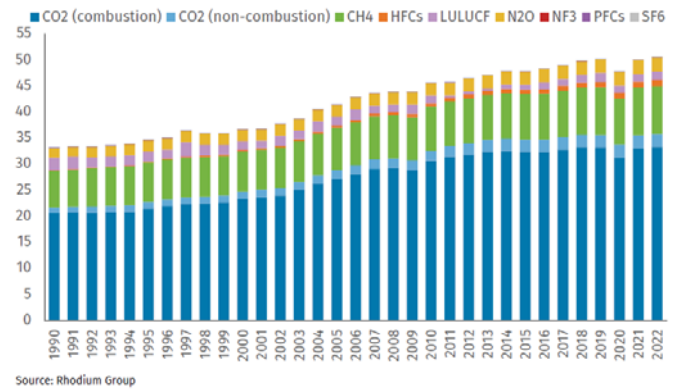


Figure 2: Global Greenhouse Gas Emissions from 1990 to 2022 (<https://rhg.com/research/global-greenhouse-gas-emissions-2022/>) [5].

Table 1: Effects of climate change on C<sub>3</sub> and C<sub>4</sub> weeds.

Climate change parameters	C <sub>3</sub> weeds	C <sub>4</sub> weeds	References
Elevated CO <sub>2</sub>	Good stimulation of photosynthesis and growth	Lesser stimulation of photosynthesis and growth	Zelikova, et al. [7]
Elevated temperature	A decrease in net photosynthesis and an increase in photorespiration	Stimulation of photosynthesis and growth at high CO <sub>2</sub>	Mahajan, et al. [8]

or C<sub>4</sub> crops (such as grain sorghum). Temperature changes significantly influence plant growth rates and phenological development in certain crops [9].

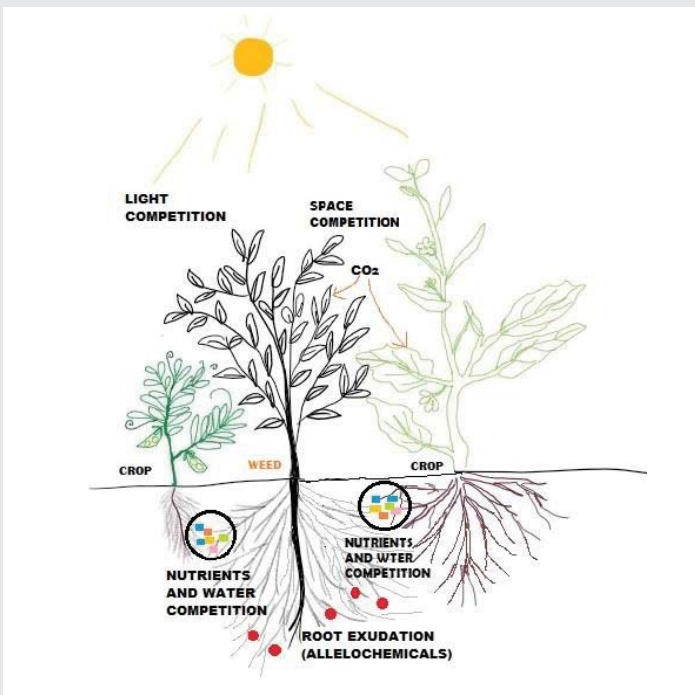
Weeds with C<sub>3</sub> and C<sub>4</sub> photosynthetic pathways respond differently to elevated CO<sub>2</sub> levels due to their distinct photosynthetic biochemistry (Table 2). Unlike C<sub>3</sub> plants, C<sub>4</sub> plants experience a smaller impact on net photosynthetic rates from higher CO<sub>2</sub> concentrations. Many C<sub>3</sub> weeds exhibit significant growth increases with elevated CO<sub>2</sub>, leading to considerable reductions in the yields of competing crops. Ziska [10] observed a 65% increase in the biomass of the C<sub>3</sub> weed, common lambsquarters (*C. album* L.), which corresponded with a 39% decrease in soybean seed yield under elevated CO<sub>2</sub> concentrations.

### Crop weed competition

In arable crops or agricultural fields, competition arises between crops and weeds due to limited resources such as water, light, space, and nutrients. This competition often results in detrimental effects on the desired crop, leading to reduced growth, hindered development, and yield losses [11]. The extent of competition and the weed's ability to interfere depend on various factors, including the specific weed species present, their density in the crop field, the competitive capacity of the cultivated crop variety, its planting density, and the prevailing environmental conditions (Figure 3). Conducting studies that examine the effects of weed interference through competition can provide valuable insights for effective weed management strategies. These studies offer crucial information

**Table 2:** Response of higher CO<sub>2</sub> concentration in weeds and crops

C <sub>4</sub> weeds vs. C <sub>3</sub> crops		
C <sub>4</sub> weeds	C <sub>3</sub> crops	Favoured under elevated CO <sub>2</sub>
Amaranthus retroflexus	Soybean	Crop
Echinochloa glabrescens	Rice	Crop
Sorghum halepense	Soybean	Crop
C <sub>3</sub> weeds vs. C <sub>4</sub> crops		
C <sub>3</sub> weeds	C <sub>4</sub> crops	Favoured under elevated CO <sub>2</sub>
Abutilon theophrasti	Sorghum	Weed
Xanthium strumarium	Sorghum	Weed
C <sub>4</sub> weeds vs. C <sub>4</sub> crops		
C <sub>4</sub> weeds	C <sub>4</sub> crops	Favoured under elevated CO <sub>2</sub>
Amaranthus retroflexus	Sorghum	Weed
C <sub>3</sub> weeds vs. C <sub>3</sub> crops		
C <sub>3</sub> weeds	C <sub>3</sub> crops	Favoured under elevated CO <sub>2</sub>
Chenopodium album	Soybean	Weed
Taraxacum officinale	Lucerne	Weed
Weedy red rice	Rice	Weed

**Figure 3:** Weed Competition and Interference in Crops.

to guide measures aimed at mitigating the impact of weeds on crop performance.

Elevated CO<sub>2</sub> levels can influence the growth rates of crops and weeds by changing global temperature, precipitation, and radiation patterns. Higher CO<sub>2</sub> levels directly impact photosynthetic activity and the competitive dynamics between crops and weeds, potentially altering weed distribution patterns [12]. Increased CO<sub>2</sub> can benefit either crops or weeds within the same field. For example, in a grass weed–crop (lucerne) scenario, lucerne growth improved with higher CO<sub>2</sub> levels. Conversely, in a sorghum field, the growth of redroot pigweed

was favoured by increased atmospheric CO<sub>2</sub> [13]. Research indicates that broadleaf C<sub>3</sub> weeds are more likely to thrive at elevated CO<sub>2</sub> levels. The impact of elevated CO<sub>2</sub> on crop–weed competition is also affected by temperature. Elevated CO<sub>2</sub> can influence nutrient dynamics between crops and weeds, as seen in a study where rising CO<sub>2</sub> levels altered competition between rice and barnyard grass in favour of rice [14]. Under higher CO<sub>2</sub>, rice exhibited greater nutrient uptake and tissue concentrations of C, N, P, and K, which enhanced its tillering, leaf area index, net assimilation rate, and biomass.

### Adaptive mechanism of weeds

There are different ways used by weeds to adapt to different changing climatic conditions or any stress conditions for their survival. These are:

**Life history strategies:** Changes in management practices, such as the transition from conventional tillage to reduced tillage, have been observed to influence the life strategies of weeds. Under reduced tillage conditions, there is a shift towards the predominance of perennial weeds. Researchers have noted a higher prevalence of broad-leaved and perennial weeds in reduced tillage systems compared to grass-type weeds. Similarly, climate change has also contributed to the emergence of new weeds that may pose greater challenges in terms of control. The changing climate creates new ecological niches that are favourable for the establishment and growth of weed species or genotypes with different life histories, well-suited to the prevailing climatic conditions.

One crucial attribute of weeds as pioneer species is their ability to disperse, which is often linked to their plant size. Elevated carbon dioxide (CO<sub>2</sub>) concentrations have been found to increase plant size. For instance, studies have reported enhanced growth of *Cirsium arvense* (Canada thistle), a common weed, when exposed to elevated CO<sub>2</sub> levels of 719 μmol mol<sup>-1</sup> compared to the ambient levels of the early 21<sup>st</sup> century. This two-fold increase in CO<sub>2</sub> concentration indicates that climate change has contributed to the significant increase in the dispersal of *Cirsium arvense*. The elevated CO<sub>2</sub> levels promote plant growth and larger plant size, leading to increased seed production. Additionally, taller plants benefit from aerodynamic factors, allowing them to disperse more seeds. This suggests that the dispersal of *Cirsium arvense* has been greatly influenced by the era of climate change, where higher CO<sub>2</sub> concentrations have facilitated enhanced growth, larger plants, and subsequently, increased dispersal through seed production.

**Rapid evolution:** Weeds, known for their resilient nature, undergo rapid evolution under changing climatic conditions, especially those with high seed production capacity [15]. This rapid evolution poses significant challenges in weed management efforts. Moreover, numerous studies provide ample evidence of weeds developing resistance against herbicides, highlighting their ability to adapt and evolve rapidly [16]. Human activities contribute to the introduction of alien plants into new habitats with varying climatic and abiotic conditions. Observing their adaptation to these local



conditions is fascinating. A meta-analysis of 134 plant species comparing native and invasive species, revealed that invasive plants exhibit a notable ability to adjust to local conditions comparable to their native counterparts. This adaptability serves as a strong indicator of their ability to swiftly evolve and thrive in novel environments [17].

**Epigenetics:** In addition to rapid evolutionary responses, alien weed species can also exhibit quick adaptive changes in their gene expression in response to environmental conditions. Environmental factors i.e. temperature, light, water availability, and salinity impose various stresses on plants, necessitating their ability to dynamically adapt. To maintain flexibility, plants employ epigenetic modifications, which involve alterations in chromatin structure without altering the DNA sequence itself. Chromatin comprises DNA sequences wrapped around histone proteins, forming a compact and organized higher-order structure. This structure can be influenced by abiotic environmental stimuli, leading to changes in gene expression, particularly at the transcriptional level.

Epigenetic modifications in plants involve three primary types i.e. histone variants, histone modifications, and DNA methylation. The structure of chromatin, where DNA wraps around histone proteins, determines DNA accessibility to transcription factors, influencing gene expression. One mechanism through which chromatin structure can be altered is by incorporating histone variants, which are closely related proteins with distinct amino acid sequences. These variants have varying affinities for DNA and binding proteins, impacting chromatin compaction. For instance, in *Arabidopsis*, the linker histone variant H1.3 plays a role in enhancing the plant's response to combined light and water stress. A study by Rutowicz, et al. [18] found that plants with the H1.3 variant showed significant changes in gene expression, increased growth rate, enhanced photosynthetic capacity, and higher stomatal density compared to wild-type plants. In conclusion, epigenetic modifications in plants, including the incorporation of histone variants, serve as crucial mechanisms for dynamic responses to environmental cues. These modifications can lead to changes in chromatin structure, influencing gene expression and facilitating plant adaptation to various stresses. The specific histone variant H1.3 in *Arabidopsis*, for example, has been associated with improved responses to combined light and water stress, resulting in enhanced growth and photosynthetic capabilities. Understanding the role of epigenetic modifications in plant adaptation to changing environments contributes to our knowledge of plant resilience and provides insights for agricultural and ecological management strategies.

**Herbicide resistance:** Herbicide resistance is the inherited ability of a particular plant to endure the application of a herbicide that would typically be lethal to a normal population of the same species. It is crucial to emphasize that herbicide resistance does not indicate an inadequacy in the herbicide's effectiveness. Resistant weeds frequently have the ability to withstand herbicide applications at levels considerably exceeding the recommended dosage.

The phenomenon of herbicide resistance is further exacerbated by climate change, which facilitates the dissemination of resistant biotypes and contributes to their widespread development. Climate change significantly contributes to the dissemination of resistant weed seeds, leading to their increased prevalence at both local and regional levels. This dissemination occurs through two primary mechanisms: spatial dissemination, involving wind dispersal or transportation via farm machinery or other means, and temporal dissemination, facilitated by persistent seed banks or bud banks, particularly in the case of perennial weeds [19]. Herbicide-resistant weeds have become a global concern, spreading extensively across different regions. A prominent example of a weed species benefiting from both herbicide selection pressures and climate change is *Bassia scoparia* (L.) A. J. Scott, commonly known as kochia. This weed species exhibits widespread herbicide resistance, particularly against glyphosate, highlighting the urgent need to address the issue. The proliferation of herbicide resistance in weeds demands increased attention and effective management strategies to mitigate its impact. By understanding the mechanisms driving resistance and considering the combined effects of herbicide selection and climate change, we can develop more sustainable approaches to weed control and safeguard agricultural systems. Targeted interventions and integrated weed management practices are crucial to combat the spread of herbicide-resistant weeds and protect crop productivity in the face of these ongoing challenges.

**Herbicide tolerance:** Herbicide tolerance refers to a species' inherent capability to survive and reproduce despite exposure to herbicide treatment at a normal usage rate. Unlike herbicide resistance, there is no selection involved as the species naturally possesses tolerance traits. While concerns about the potential evolution of tolerance into resistance exist, this section specifically explores the impact of changing climate conditions on herbicide tolerance. A study by Benedetti, et al. [20] examined the impact of changing climate conditions on the herbicide tolerance of *Echinochloa colona*, commonly known as jungle rice. The study involved subjecting jungle rice plants to repeated herbicide low doses under two heat stress levels (30°C and 45°C). The findings revealed that several genes in *Echinochloa colona* were upregulated, indicating an increase in herbicide tolerance. The results highlight the influence of changing climatic conditions, particularly heat stress, on the expression of genes associated with herbicide tolerance in jungle rice. These findings suggest that under elevated temperature regimes, certain genes in *Echinochloa colona* are activated, potentially enhancing the species' ability to withstand herbicide treatments. Understanding the mechanisms by which changing climatic conditions interact with herbicide tolerance is crucial for effective weed management strategies. Continued research is necessary to elucidate the specific genetic pathways and physiological processes involved in the development and expression of herbicide tolerance in response to climate change. By gaining insights into the molecular and physiological responses of weeds to changing environmental conditions, we can better anticipate and address the challenges posed by herbicide tolerance. Such knowledge will enable

the development of sustainable weed control strategies that consider the evolving interactions between climate change and herbicide tolerance, ultimately supporting effective weed management and preserving agricultural productivity.

In another study, Matzrafi, et al. [21] evaluated the efficacy of different herbicides using two strains of *Brachypodium hybridum*. The strains used were BrI-638, which was sensitive to herbicides, and BrI-782, which exhibited resistance. The herbicides tested in the experiment were malathion and pinoxaden. The results revealed that as the temperature increased up to 28/34°C (day/night), the resistant strains of *Brachypodium hybridum* showed nearly 100% survival even when exposed to half doses of the herbicides. However, when higher doses of herbicides were applied, either individually or in combination, and the temperature was raised, the survival rate of the resistant strains decreased to approximately 30%. These findings suggest that as the temperature rises, the efficacy of the herbicide declines, particularly for the resistant strains of *Brachypodium hybridum*. The reduced effectiveness of the herbicides at higher temperatures indicates a potential challenge in weed management, as elevated temperatures may compromise the control measures.

Understanding the impact of temperature on herbicide efficacy is vital for optimizing weed control strategies. Further research is necessary to explore the underlying mechanisms behind the reduced efficacy of herbicides at elevated temperatures and to develop alternative approaches that can overcome this challenge. By considering the interaction between temperature and herbicide resistance, we can enhance weed management practices and mitigate the potential impact of rising temperatures on herbicide effectiveness.

**Cropping systems vulnerability:** As the climate continues to change, it brings forth various challenges that demand swift adaptation, with some changes becoming irreversible. One critical tipping point is observed in cropping systems, where the need for rapid adjustment arises. The anticipated rapid adaptations in the changing climate pose a significant challenge for crop variety development [22]. Additionally, climate change introduces greater unpredictability in pest control within existing cropping systems. To address these vulnerabilities, the implementation of more sustainable cropping systems is essential. Practices such as reduced tillage, cover crops, crop rotations, diversification, intercropping, mulching, and the cultivation of perennial crops offer potential solutions [23–25]. By adopting these practices, we can mitigate the negative impacts of climate change and enhance the resilience of agricultural systems.

Under changing climate conditions, selecting suitable crops that exhibit flexibility in adapting to varying environmental conditions becomes crucial. The choice of crops to be cultivated under different climates will inevitably influence the distribution of weed occurrences. It is worth noting that  $C_4$  weeds, known for their competitive nature, have been predominant in warmer regions, while  $C_3$  weeds have thrived in cooler temperate zones. However, an increased mixture of  $C_4$  and  $C_3$  weeds within a given region may lead to heightened weed

competition with crops [26]. In summary, the changing climate necessitates the adoption of sustainable cropping systems and careful selection of crop varieties that can effectively adapt to evolving environmental conditions. By implementing these strategies, we can address the challenges posed by climate change and mitigate the impact of weed competition on crop production.

**Co-evolution with human management:** Back in 1956, John Harper, widely regarded as the pioneer of modern weed ecology, astutely observed that "arable weeds constitute an ecological group that has been selected by the very practices that were originally designed to suppress them." Ironically, by confining agronomic fields within greenhouses, we inadvertently create a greenhouse effect, subjecting these fields to a favourable environment. This controlled environment often leads to a flourishing of insect pests and pathogens, surpassing what would typically occur under outdoor conditions exposed to extreme weather. However, unlike other pests, weeds are not usually a major concern within greenhouses since they do not have a tendency to invade *en masse*. Nevertheless, as global temperatures rise in temperate regions, weeds are taking advantage of the warmer conditions and exhibiting other adaptations, such as developing herbicide resistance in response to elevated CO<sub>2</sub> levels.

It is crucial to recognize and address the multifaceted challenges posed by this changing landscape. By understanding the unintended consequences of our weed control practices and the complex interplay between climate change and weed dynamics, we can develop more effective strategies for sustainable weed management in the face of evolving environmental conditions. This requires a holistic approach that considers the broader ecological implications and aims to strike a balance between weed control and maintaining the overall health and productivity of agronomic systems.

**Riding the climate change storm:** The impact of climate change on storm frequency and severity is undeniable, as documented by Tamarin-Brodsky and Kapsi [27]. These storms, in turn, affect various forms of life, but it is the resilient organisms such as weeds and invasive species that often emerge as the most tenacious survivors. An illustrative example of this resilience can be seen in the aftermath of Tropical Storm Irene in 2011, where Japanese knotweed capitalized on the fragments spread by the storm's destructive force, thereby expanding its distribution in Vermont [28]. Similarly, *Carex kobomugi* Ohwi, an invasive sedge, thrived following Hurricane Sandy in 2012, outperforming the native coastal grass American beachgrass. These instances highlight the capacity of invasive species to exploit the disturbances caused by storms, using them as opportunities for colonization and proliferation. As climate change continues to leave its mark on our planet, the consequences could manifest in the form of a "Planet of weeds," as previously alluded to by Quammen [29].

However, it is crucial to recognize the broader implications of such transformations. A planet extensively scarred by climate change and overrun by invasive species could have far-reaching ecological and socio-economic consequences.



Therefore, it is imperative that we understand and address the underlying factors contributing to the success of these opportunistic species. By developing comprehensive strategies that consider the interconnectedness of climate change, storm events, and invasive species dynamics, we can work towards mitigating the negative impacts and promoting the resilience of native ecosystems.

## Conclusion

The present era of climate change is characterized by rising temperatures and increased CO<sub>2</sub> levels, which have significant implications for crop growth, productivity, and resource use efficiencies. Among various pests, weeds are responsible for the highest yield losses, accounting for 34% of total losses, while losses due to insect pests and diseases are comparatively lower at 18% and 16% respectively. The differential responses of weeds with C<sub>3</sub> and C<sub>4</sub> photosynthetic pathways to higher CO<sub>2</sub> levels and temperatures can greatly influence the dynamics of crop-weed competition. In South Asia, weed competition has led to substantial yield losses in crops such as rice (183 kg/ha) and wheat (up to 88 kg/ha). In India alone, weeds have caused an economic loss of approximately 10 billion USD across ten major crops. Groundnut (35.8%), soybean (31.4%), green gram (30.8%), pearl millet (27.6%), maize (25.3%), sorghum (25.1%), sesame (23.7%), mustard (21.4%), direct-seeded rice (21.4%), wheat (18.6%), and transplanted rice (13.8%) are the crops most affected by weed-related losses. Given these significant economic and agricultural impacts, it is crucial to understand and assess the combined effects of multiple climatic factors and their complex interactions on the crop-weed interface. Such understanding is essential for formulating effective weed management strategies that can adapt to changing climate scenarios. By comprehensively examining the interactions between climatic factors and weeds, we can develop strategies like integrated weed management, planting resilient crop varieties, adjusting planting dates, implementing site-specific weed management, using allelopathic plants, rotating and mixing herbicides, and employing mulching and tillage practices to mitigate yield losses and minimize economic damage caused by weeds in various crops. This requires considering the intricate relationships between temperature, CO<sub>2</sub> levels, and weed dynamics, as well as their impacts on crop growth and competition.

In conclusion, the simultaneous changes in multiple climatic factors pose challenges for crop-weed management under climate change. By gaining a deeper understanding of these complex interactions, we can develop targeted and adaptive strategies to effectively manage weeds and reduce their detrimental effects on crop productivity, thereby ensuring food security and sustainable agriculture in the face of changing climatic conditions.

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## Add-on Information

**Authors' contribution:** R. Kaur: Think of the idea, conceptualization, curation of resources, reviewing and editing; S. Kumar: Writing original draft and drawing figures; S.A. Ali: Drawing figures, writing, reviewing and editing; S. Kumar, U.M. Ezing, R.S. Bana, A Dass, S L Meena and T. Singh: Made suggestions and revised the manuscript. All authors confirmed and approved the final manuscript.

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