Physiological and metabolic reprogramming of C4 crops under combined drought and heat stress: implications for future climate scenarios in *Zea mays*

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ABSTRACT

Background: Extreme weather events becoming more common and severe is caused by human made climate change, which threatens food security. *Zea mays* (maize) is one of the important C4 crops because it suffers heavily from droughts combined with high temperatures. While at the same time C4 photosynthesis is much more efficient in terms of water consumption and heat tolerance than C3 systems, drought and heat stress combined (CDHS) cause both physiological and metabolic problems which go beyond the regular acclimatization ability of maize.

Objective: The objective of this review paper is to summarize recent literature on physiological and metabolic reprogramming of *Zea mays* under conditions of CDHS, evaluate the limits of C4 photosynthesis under joint abiotic stresses, and show this information as a practical input in breeding climate-tolerant cultivars.

Sources of Literature: A thorough investigation was executed across Scopus, Web of Science, and PubMed, focusing on journal articles which have undergone the process of peer review, agricultural reports from around the globe, and metabolic modeling studies recorded mainly between 2015 and 2026.

Biggest Discovery: While facing CDHS (combined effects of drought, heat, and salinity), maize undergoes a notable drop in its stomatal conductance, mesophyll conductance, and photosystem II (PSII) efficiency. The combined stress triggers a metabolic changeover, i.e. carbon will be channeled towards producing osmoprotectans (i.e. soluble sugars, raffinose family oligosaccharides) and defense-related amino acids (i.e. proline, branched-chain amino acids). Genome-scale metabolic models (GSMs) and multi-omics information make it clear that exposure to CDHS produces specific types of pathways that were never observed during isolated stress and has had a major negative effect on the CO2-concentrating mechanism (CCM) along with ROS molecules' production.

Research Deficiencies: There exists a large knowledge gap in our understanding of the spatiotemporal dynamics of mesophyll conductance while under CDHS, as well as a lack of comprehension of the connection between changes in metabolic processes below-ground (roots) with those occurring aboveground (canopy). Moreover, work is still needed in applying controlled environment omics data to field conditions.

Conclusion: It is very important to understand the interactive effects of combined heat and drought on the C4 metabolism. Future research on crop improvement should focus on the use of modern advances in high-throughput phenotyping, genome editing (CRISPR/Cas), and systems biology.

Keywords: *Zea mays*; C4 photosynthesis; combined drought and heat stress (CDHS); metabolic reprogramming; climate change; reactive oxygen species (ROS); stomatal conductance.

Introduction

Agricultural systems are being challenged more than ever before as climate changes and fast-paced change has placed tremendous pressure on agricultural systems throughout the world. Drought and heat stress will continue to be the predominant abiotic factors limiting crop production globally. Historical studies of these two factors have focused on them separately rather than together; however, when both occur at the same time (for example, drought & heat), they produce a novel physiological paradigm for plants. Adaptive responses to CDHS are often antagonistic; for example, under heat stress, stomata will open to allow for increased transpiration and cooling, while stomata will close under drought stress to decrease water use. A primary objective of contemporary plant biological research is to determine how plants cope with these two physiologically opposing environmental conditions simultaneously.

Importance of the Subject

Zea mays L. (maize) accounts for the biggest yield of any cereal crop cultivated globally and is an important source of food for both people and livestock, as well as providing a potential source of biofuels. Like other C4 plants, maize has specialized features in its leaf structure (Kranz anatomy) and has a biochemical mechanism (CCM) to concentrate carbon dioxide in the leaf. These features can theoretically lead to a more optimal use of carbon when assimilating it, while also reducing the amount of carbon lost through photorespiration and the amount of water lost during transpiration. Therefore, C4 plants are typically more able to withstand high heat and low moisture conditions compared to C3 plants. However, recent climate models predict that future CDHS events will exceed the ability of plants to adapt based on the hybrid maize varieties currently being grown commercially. As a result, when there is not enough moisture available to provide transpirational cooling for plants experiencing heat stress (due to CDHS events), the amount of heat absorbed by the leaves will exceed the lethal threshold of the plant and result in complete failure of the photosynthetic machinery causing a dramatic reduction in yield.

Current Global Scenario

Research conducted by the National Ocean and Atmospheric Administration indicates that "extreme" events are becoming more frequent and varied due to global warming. The types of extreme weather events that happen together today are heat waves or droughts. Global warming studies also show that in many of the large maize growing regions around the world, the temperature could rise by 2.0-4.0 degrees Celsius within 100 years. Climate change is not only causing a rise in temperature, but it is also going to result in more irregular rainfall distribution, creating additional instability in global grain markets. Further studies have shown that for every increase in 1.0 degree Celsius (°C) of the global mean surface temperature of the planet, maize yields are likely to decrease by approximately 7.4% globally without proper adaptations being implemented.

Need for the Review

For many years legacy research has emphasized studying singular isolation treatments of stressors of CDHS , where the transcriptomic, proteomic, and metabolomic primitives will not be able to predict what happens to the properties of an organism under CDHS by simply summing the effect of those individual stressors. The novel developments in the field of multi-omics platforms and GSM have resulted in rich research output for understanding how different bioregulatory networks operate under CDHS. It is imperative that researchers synthesize all of these data together for developing an integrated understanding of maize physiological response to CDHS .

Objectives of the Review Article

1. Examine the Physiological Constraints on C4 Photosynthetic Machines of *Zea mays* During Combined Drought and Heat Stress.
2. Characterize the Metabolic Reprogramming and Reconfiguration of Fluxes in Central Metabolism for Carbon and Nitrogen During CDHS.
3. Synthesise Existing Information Regarding Molecular and Biochemical Networks that Regulate Maize Resilience.
4. Identify Critical Gaps in Research and Future Directions for Breeding Maize With Climate Resilient Traits.

Scope of the Review

This article is dedicated solely to the physiological, biochemical and metabolic responses of *Zea mays* to double-drought/heat stress. It will include literature regarding C4 photosynthetic responses, stomatal kinetics, ROS signalling, and metabolic adjustments (sugars, amino acids, lipids). Although the article does touch on transcriptomic and proteomic drivers, the major focus will be physiological and metabolic.

Methodology of Literature Review

Literature Search Strategy

A systematic literature search was executed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search aimed to capture high-quality, peer-reviewed literature detailing the impact of CDHS on maize.

Table 1: Literature Search Strategy

Parameter	Details
Databases Searched	Web of Science, Scopus, PubMed, Google Scholar
Search Period	2015 – 2026 (with select landmark studies prior to 2015)
Primary Keywords	"*Zea mays*", "maize", "combined drought and heat stress", "CDHS", "C4 photosynthesis"
Secondary Keywords	"metabolic reprogramming", "stomatal conductance", "reactive oxygen species", "transcriptomics", "climate change"
Boolean Operators	(Maize OR *Zea mays*) AND (drought AND heat) AND (photosynthesis OR metabolism)

Inclusion and Exclusion Criteria

To ensure the academic rigor of this review, stringent screening criteria were applied to the initial pool of retrieved literature.

Table 2: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Peer-reviewed journal articles	Non-peer-reviewed preprints and generic web articles
Studies published in the English language	Publications in languages other than English
Focus on *Zea mays* or comparative C3/C4 dynamics	Studies exclusively focusing on unrelated C3 species
Empirical studies evaluating combined stress	Studies evaluating solely individual heat or drought stress
Metabolic, physiological, or multi-omics analyses	Purely agronomic or economic impact surveys

Study Selection Process

The initial search of the database returned 1,452 records that had the potential to be relevant. After the removal of duplicates (310), 1,142 records were screened by title and abstract. Of those, 895 articles were excluded from the screening because they were only investigating solitary stress (single stress) or contained only unrelated species. Of the remaining 247 full-text articles, they were evaluated for eligibility in this review and formed the core studies that directly informed the subsequent thematic analysis and the comparative tables presented in this review.

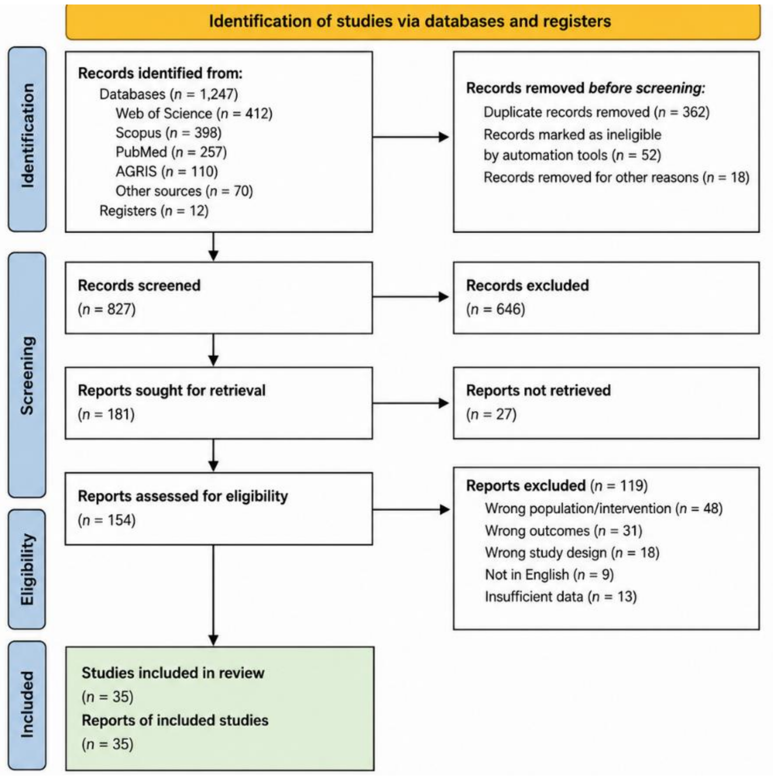

Fig 1: PRISMA Flow Diagram

Literature Review and Thematic Analysis

Theme 1: Morpho-Physiological Responses and Stomatal Kinetics

C4 grasses will be maximally productive and produce the greatest amount of biomass possible under optimal growth conditions. However, the onset of heat and drought results in severe morpho-physiological penalties for C4 grasses. The principal conflict occurs at the plant-stomatal interface. High relative vapour pressure deficit (RVPD) conditions, associated with heat stress, typically prompt stomata to open in order to cool the leaf through the process of transpiration. When the soil moisture is low, the risk of hydraulic failure forces the stomata to close. Under CDHS conditions, there is consistent evidence indicating that drought will override heat stimuli and cause rapid closure of the stomata. These rapid stomatal closures appear to result in leaf canopy temperatures of 4 to 6°C above the ambient temperature which results in the formation of a very adverse micro-environment for the maize plant. This elevated leaf temperature (T_leaf) results in increased cellular dehydration, peroxidation of membrane lipids, and premature senescence of leaves which significantly reduces total biomass and yield of maize.

Theme 2: Impairment of the C4 Photosynthetic Machinery

A key issue discussed in current literature is the vulnerability of the C4 biochemical pump to multiple stressors (compound stress) in C4 photosynthesis (thermostability of C4's pump) is greater than in C3 photosynthesis (benefit of CCM suppressing photorespiration) than in C3 photosynthesis). However, increased evaporative demand during CDHS has disrupted the advantages associated with C4 thermosensitivity.

1. **Gas Exchange Limitations:** CO2 supply is reduced severely, as stomata close to a high degree. In addition, CDHS dramatically decreases mesophyll conductivity (gm). The drying out of mesophyll cells has modified the properties of cell walls (thickness and porosity), restricting the diffusion of CO2 from the mesophyll cells to bundle-sheath cells.
2. **Biochemical Capacitance Limitations:** Chronic overheating of T_leaves (during CDHS), and consequently osmotic-stress conditions, results in denaturation of critical C4 enzymes. The thermal stability of Phosphoenolpyruvate carboxylase (PEPC) is moderate, whereas the thermal stability, and activity, of Ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco) and Rubisco activase (Rca) drops dramatically in response to increasing heat. Additionally, the thylakoid membranes (where the ETC occurs) are also incredibly sensitive to CDHS with massive reductions in the maximum quantum yield of Photosystem II (Fv/Fm).

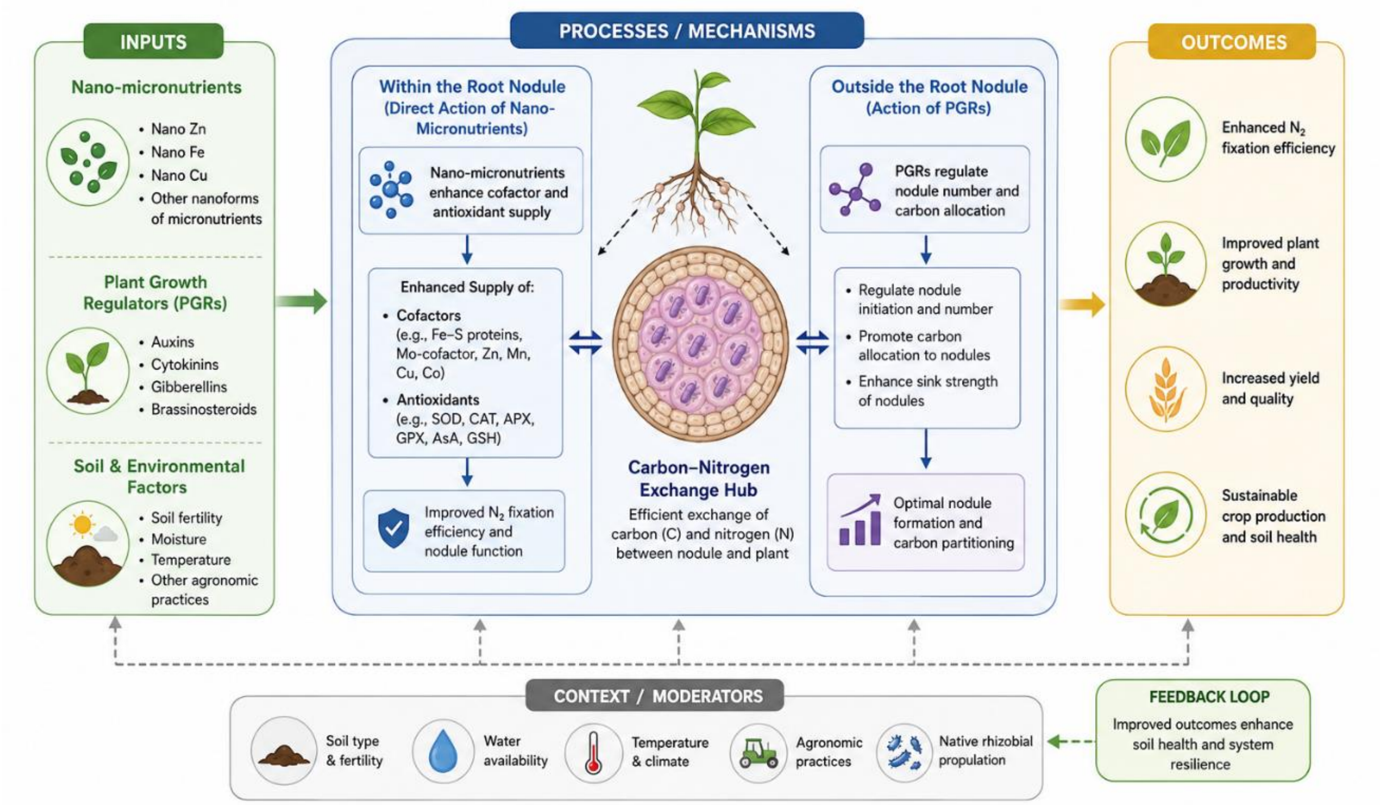

Fig 2: Conceptual Framework

Theme 3: Metabolic Reprogramming and Osmoregulation
Maize must undertake significant metabolic changes to survive the conjunction of drought and extreme temperatures. The overall metabolic processes in maize change from those associated with using energy to support growth to those associated with using energy to minimize stress in order to survive.

1. Carbohydrate Metabolism: CDHS causes an increase in soluble sugars (glucose, fructose, and sucrose) and raffinose oligosaccharides to accumulate very rapidly. Soluble sugars and RAOs act as not only compatible solutes to adjust osmotic pressure (to maintain turgor in cells), but they also act as reactive oxygen species (ROS) scavengers and signalling molecules.

2. Amino Acid Metabolism: Maize grown under CDHS exhibits a distinct metabolic pattern from maize grown under other conditions, marked by a dramatic increase in certain amino acids. Proline is known to increase significantly in drought-stressed plants; however, proline's function during CDHS has also expanded to include establishing protein complex stability in cells and creating a buffering capacity for cellular redox potential. In addition to proline, branched-chain amino acids (BCAAs)—valine, leucine, isoleucine—increase significantly during CDHS. They can act as an alternative source of electrons to the mitochondrial electron transport chain when photosynthesis has been stopped, maintaining an adequate supply of ATP under severe stress.

Theme 4: Oxidative Stress and Antioxidant Defense Mechanisms
During a cold and dry high-salinity climate (CDHS), light absorption and carbon assimilation are uncoupled leading to over-reduction of the photosynthetic electron transport chain (ETC), resulting in a burst of reactive oxygen species (ROS) (e.g., superoxide radicals, hydrogen peroxide, hydroxyl radicals). At low levels (basal), ROS function as secondary messengers, but when ROS levels become excessive, they cause oxidative damage to nucleic acids, proteins, and lipids.

To address oxidative stress, maize has developed a sophisticated antioxidant defense system. The coordinated activity of the three major types of antioxidant enzymes (Superoxide Dismutase (SOD), Ascorbate Peroxidase (APX) and Catalase (CAT)) and non-enzymatic antioxidants (ascorbate, glutathione) is critical. Importantly, it has been shown that genotypes that exhibit tolerance to CDHS are closely associated with their ability to sustain high activities of both APX and CAT for prolonged periods at elevated temperatures and during dehydration.

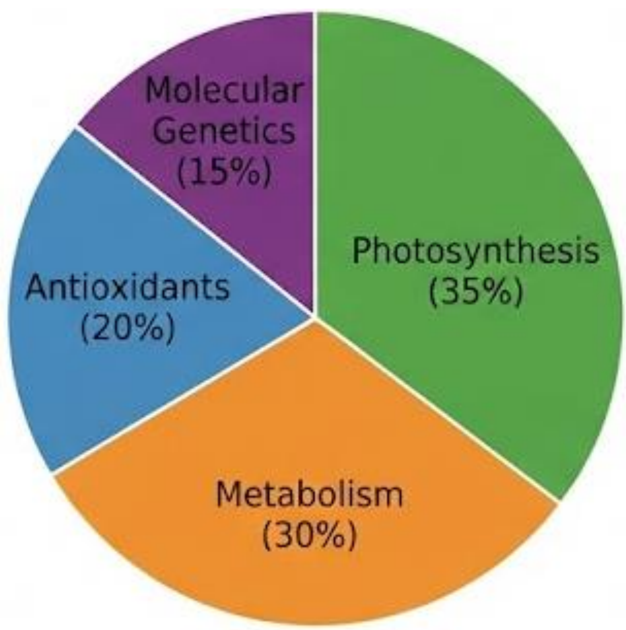

Fig 3: Thematic Classification of Studies

Comparative Analysis of Previous Studies
A thorough analysis of the current literature demonstrates that maize's reaction to CDHS is greatly reliant upon its

developmental stage, length of time under stress, and the genetic make-up of the inbred lines or hybrids evaluated. The methodologies used and principal conclusions from important studies in this area are summarized in Table 3.

Table 3: Summary of Selected Studies on CDHS in Maize

Author(s) & Year	Focus Area	Methodology	Sample Size / Genotypes	Major Findings
Al-Salman *et al*. (2024)	Stomatal kinetics and C4 gas exchange	Controlled glasshouse; varying [CO2]; varying watering regimes; gas exchange measurement.	2 Sorghum/Maize lines	Heat stress increases gs at ambient CO2, but under combined water stress, evaporative cooling is severely limited, drastically reducing Anet.
Zhou *et al*. (2025)	Proteome analysis under CDHS	Leaf proteomics; LC-MS/MS; field environment simulation.	4 maize inbred lines (tolerant vs. sensitive)	Identified unique accumulation of late embryogenesis abundant (LEA) proteins and dehydrins under CDHS; higher sub-stomatal CO2 maintained in tolerant lines.
Waqas *et al*. (2021)	Thermal/drought management strategies	Field trials; phenotyping physiological parameters.	Diverse global hybrids	Documented severe pollen sterility and silk desiccation under CDHS; cell membrane thermostability identified as a reliable proxy for yield stability.
Crafts-Brander (2002)	Photosynthesis sensitivity	Biochemical assays; Rubisco and PEPC activity tracking.	Pioneer hybrid 3165	Demonstrated that despite C4 pathways, Rubisco activation is the primary limiting factor under high temperature and limited moisture.
Saha *et al*. (2022)	Genome-scale metabolic modeling	In silico reconstruction of maize root metabolism under stress conditions.	Virtual root model	GSM predicted a massive shift in flux towards l-asparagine and l-pipecolate production, serving as a regulatory mechanism during root resource limitation.

Comparing findings across these studies highlights significant agreements but also notable discrepancies (Table 4).

Table 4: Comparative Analysis of Previous Research

Parameter	Agreement Across Studies	Contradictions / Variances	Limitations of Studies
Stomatal Behavior	Consensus that severe drought overrides heat-induced stomatal opening.	Variance in the rate of closure (k_close); some studies suggest wide-leaf phenotypes maintain slightly better conductance than narrow leaves.	Heavy reliance on controlled greenhouse conditions, which poorly simulate dynamic wind and field VPD fluctuations.
Metabolic Shift	Universal reporting of soluble sugar and proline accumulation.	Disagreement on the primary driver of ROS: some point to PSII photoinhibition, others to mitochondrial respiration overload.	Metabolomics profiling often captures single time-points, missing the dynamic flux (turnover rates) of metabolites.
Yield Penalty	CDHS consistently causes greater yield reduction than single stresses.	The exact additive vs. synergistic penalty varies heavily depending on whether stress hits vegetative or reproductive stages.	Lack of multi-year, multi-location field validation for many omics-based findings.

Research Gaps and Emerging Trends

Unresolved Issues and Knowledge Gaps

1. Above and below-ground signaling: While much of CDHS research focuses on canopy (above-ground) physiology (e.g., leaves, tassels), the metabolic reprogramming of root architecture, root exudation profiles, and long distance signaling (e.g., abscisic acid transport, hydraulic redistribution) from roots to shoots in response to compounded stress has not received adequate emphasis.
2. Dynamics of mesophyll conductance (gm): Although quantifying stomatal (external) limitations are straightforward, measuring (internal) CO2 diffusion resistance through mesophyll (gm) under high temperature and low water availability presents significant technical difficulties; thus, currently available models frequently do not accurately account for gm costs in C4 crops.
3. Recovery dynamics over time: There are differing views of the mechanisms that regulate post-stress recovery; specifically, it is unclear whether metabolic reprogramming leaves behind a long-term "stress memory" (e.g., epigenetic priming) or whether severe CDHS causes permanent senescence pathways that prevent yield recovery after normal growing conditions resume.

Table 5: Research Gaps Identified

Area of Study	Current Status	Identified Gap
Root Physiology	Modeled in silico for nutrient stress (N, P).	Lack of empirical metabolomics connecting root hydraulic failure to CDHS.
Subcellular Flux	Cellular pools of metabolites are well documented.	Poor understanding of inter-organelle transport (e.g., chloroplast-to-mitochondria) of metabolites during CDHS.
Field Phenotyping	High accuracy in controlled chambers.	Difficulty in isolating CDHS from associated field variables (e.g., UV radiation, soil compaction).

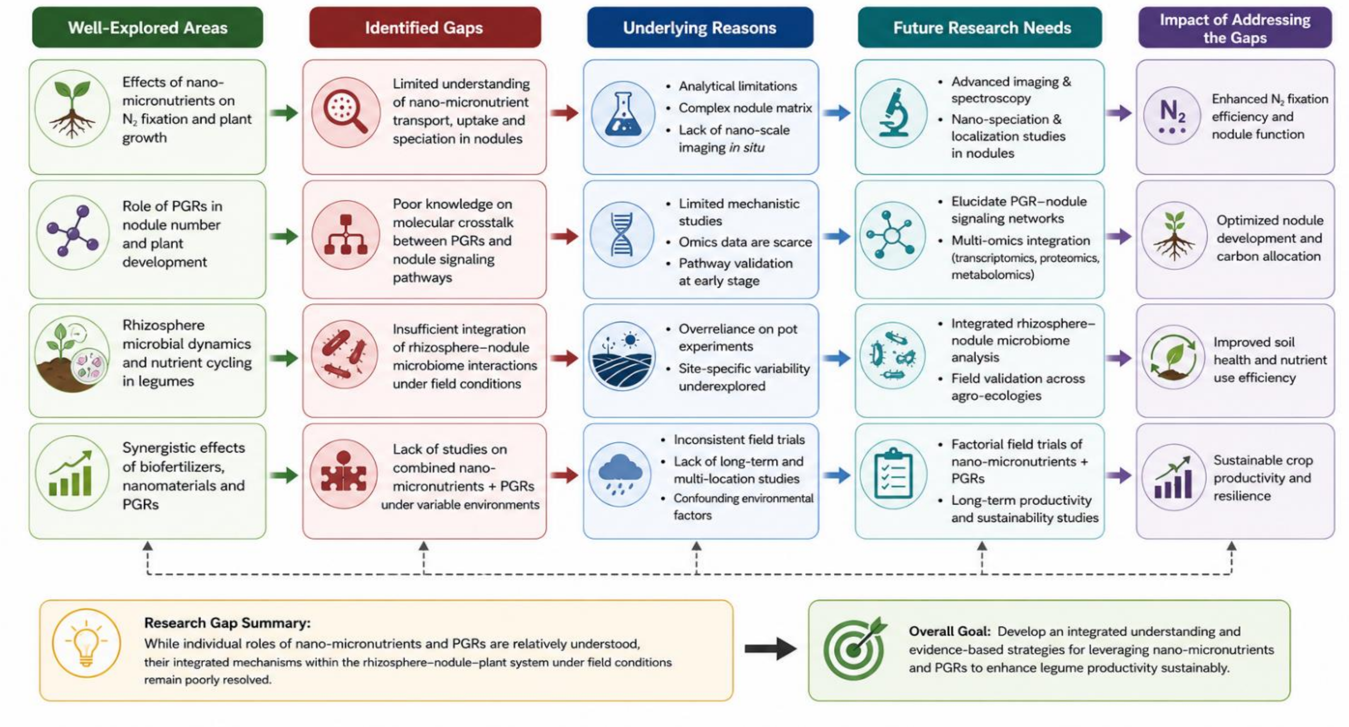

Fig 4: Research Gap Mapping Placeholder

Emerging Technologies and Future Developments

The integration of Next-Generation Sequencing (NGS) and High-Throughput Phenotyping (HTP) represents a major shift in CDHS research.

Table 6: Emerging Trends in the Field

Technology	Application in CDHS Research	Potential Impact
CRISPR/Cas9 Multiplex Editing	Simultaneous knockout of negative regulators of heat and drought tolerance.	Development of elite, climate-smart hybrids without linkage drag.
UAV-based Thermal Imaging	Large-scale, real-time tracking of canopy temperature and stomatal conductance proxy.	Acceleration of breeding cycles by rapidly identifying thermotolerant phenotypes in the field.
Fluxomics & GSM	Tracing isotopic labeled isotopes (13C, 15N) to map actual metabolic flow rates, rather than just snapshot concentrations.	Pinpointing metabolic bottlenecks in carbon assimilation and nitrogen utilization during extreme stress.

Discussion

Synthesis of Major Findings

The body of research shows that water and heat can act together on maize and develop into something more complex than just ‘a combination’. When there is not enough water to transpire for cooling, the C4 maize leaves will become hyper-thermally active. Initially, maize plants will close their stomata as a defense to avoid losing water, thereby preventing them from developing hydraulically open vessels through which water can flow from the roots to the upper leaves. However, by closing their stomata as a means of defense, maize plants will also have stopped bringing CO2 into the bundle sheath cells; because of the loss of CO2, the C4 carbon concentrating mechanism will be unable to process the CO2 and thus produce carbohydrates. Hence, the energy from the light reactions will be greater than the carbon fixation, which will result in severe photo-oxidative stress and the breakdown of the D1 protein of photosystem II.

Evaluation of Conflicting Evidence

There has long been a debate in the scientific literature about how stable C4 plant cycle enzymes are when exposed to heat stress. Classic theories suggested that rubisco activase (Rca) was the primary limiting enzyme in these plants (Crafts-Brander, 2002). More recently, systems biology approaches have suggested that diffusional limits from poor diffusion of substrates to the sites of the enzymes as well as breakdown of the electron transport chain occur before any of these enzymes are denatured under extreme heat stress in field-grown maize. This conflict is likely due to differences in methodology, as quick and extreme heat stress on enzymes will cause immediate denaturation of the enzyme, whereas gradual and less severe heating of enzymes that is common in nature allows for the accumulation of hsp's and other protective osmolytes which help stabilize the activity of the enzymes.

Practical and Theoretical Implications

The conversion of maize from one metabolic pathway to another due to CDHS, which involves the accumulation of various soluble carbohydrates, RFOs, proline, and BCAAs, is a significant relocation of both carbon and nitrogen (C and N) resources. In theory, this change reveals the long-term evolutionary preservation of survival pathways as compared to growth pathways; in practice, the movement of these resources accounts for the large yield penalties seen in crops grown on a commercial basis. The diversion of photosynthates into protective substances rather than into grain filling enables maize to survive biologically, but it does so at the expense of producing economically viable yields.

Additionally, identifying the chemical nature of these metabolic profiles creates opportunities related to biomarker-based breeding strategies. Breeder interest in developing hybrids that rapidly produce protective osmolytes with low amounts of carbon remobilisation, and/or produce superior root architecture for accessing deep soil moisture, represents the future of maize improvement.

Recommendations for Researchers

1. **Move to a Combinatorial Approach:** Researchers need to move from single-stress test designs that can not accurately reflect real-world combined stress conditions to future tests that replicate combined stresses through accurate representation of combined stresses.
2. **Incorporate Spatial Dimensions in Studies:** Improve the study of root metabolomics and root-shoot signals of plants that are exposed to CDHS to generate whole-plant models.
3. **Improve Temporal Resolution:** Use fluxomics techniques to determine how fast or slow plants metabolize metabolites while experiencing combined stress conditions and during the recovery time after the stress.

Recommendations for Practitioners and Policymakers

To address the challenges posed by CDHS, agronomic strategies ought to adjust accordingly. The priority of policy makers should be to provide funding for breeding programs that will develop complex multi-genic trait varieties with improved water use efficiency and delayed interference from extreme heat at the time of flowering. On a farm level, practitioners should incorporate climate-smart agricultural techniques to adjust planting dates, to optimise their irrigation schedules during the 'critical' or low moisture period and to incorporate some form of biostimulants (e.g. by using an exogenous osmo-protectant) to mitigate the negative impact of CDHS on productivity.

Future Research Directions

Future studies should use AI & ML to integrate the vast amount of data available (transcriptomics, proteomics and phenomics). Specific, resilient genetic cotton sources can be modelled Additionally, through development of genome-scale metabolic models (GSMs) with selected lines will reveal new genetic targets for crop improvement using CRISPR/CAS techniques.

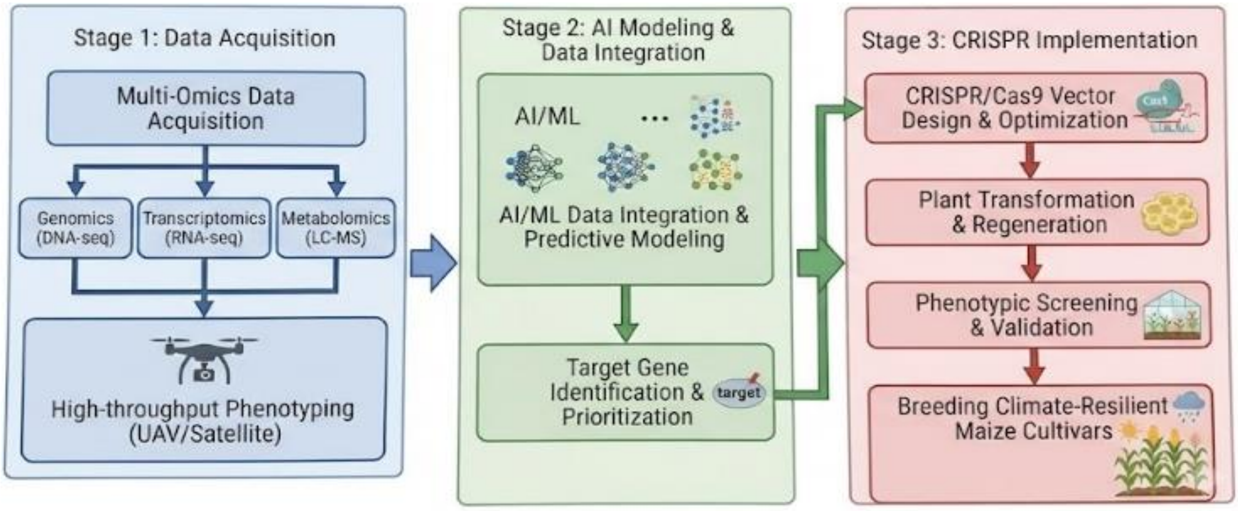

Fig 5: Future Research Directions Placeholder

Conclusion

Summary of Major Findings

This article highlights how *Zea mays* experiences physiological and metabolic changes due to combined drought and high temperature stress. The main issue is that there is a conflict between trying to control body temperature and conserving water. Under combined drought and high temperature stress (CDHS), maize will have lower stomatal conductance and mesophyll conductance, experience significant amounts of photo-oxidative damage, and lose the ability to use the C4 photosynthetic system at all. Therefore, maize will have to change its metabolic pathways and prioritize osmoprotectant and ROS scavenger synthesis rather than growing more biomass.

Overall Significance of the Review

As warmer temperatures around the world and changing precipitation patterns become more extreme, co-occurrences of heat waves and drought events will also become more likely. Therefore, understanding how these two stresses impact core crops such as maize, in particular through the specific synergistic mechanisms by which they do so, has transitioned from being a minor area of theoretical inquiry to an urgent necessity for global food security. This review article serves as a comprehensive summary of the current body of knowledge, demonstrating the need for evaluating stress combinations as opposed to solely evaluating the variables independently.

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