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# **Pearl Millet (***Pennisetum glaucum***): A Climate Resilient and Nutritionally Significant Crop for Global Food Security**

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*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

The environmental balance needed for agriculture is severely strained due to changes in rainfall patterns and climate change, as well as the growing global need for food. As global temperatures rise and precipitation patterns become more erratic, millets offer an efficient solution to the trade-off

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between food security and water availability. Millets are rich in nutrients and possess a special ability to endure extreme conditions such as heat, drought, and various other abiotic and biotic stresses. Pearl millet is a highly climate-resilient crop capable of mitigating the adverse impacts of climate change. Antioxidant gene expression, presence of a waxy outer layer and heat shock proteins/chaperons contribute to its abiotic stress tolerance. By adjusting its flowering phenology and establishing fast-growing roots, pearl millet enhances its water and nutrient use efficiency. Stable sources of germplasm in pearl millet that exhibit resistance to diseases such as downy mildew, blast, rust, smut, and ergot have also been incorporated into disease resistance breeding programs. Pearl millet plays a crucial role in nourishing the poverty-stricken populations due to its high palatability and rich nutritional profile. Various bioactive compounds pertain to hypoglycemic, anticancerous and probiotic properties that contribute to its health benefits. Biofortification in pearl millet offers a solution to address issues of micronutrient deficiency in vulnerable populations. Continued research and investment in pearl millet production not only bolster food security but also contribute to the resilience of agricultural systems in the face of increasingly unpredictable environmental conditions. Thus, embracing pearl millet represents a forward-thinking approach to ensuring food security and promoting nutritional diversity on a global scale.

*Keywords: Abiotic stress; biotic stress; climate change; food crisis; nutrition; value addition.*

#### **1. INTRODUCTION**

Agriculture plays a crucial role in enhancing global food security, especially in the face of climate change. As global temperatures rise and precipitation patterns become more erratic, millets offer an efficient solution to the trade-off between food security and climate fluctuation. An estimated 2 to 3 billion people may experience food insecurity and hunger by 2050 as a result of declining food production rates as agricultural systems struggle to adapt to rapidly shifting environmental conditions and the additional burden of feeding a population expected to surpass 9 billion [1].

The environmental balance necessary for agriculture is being severely strained not just by the increase in food demand but also by the altering temperature and patterns of precipitation. Events like more severe and frequent floods and droughts as well as irregular rainfall are clear indicators of this. Further deficits in the world's food supplies may result from the fragile balance between agriculture and climate.

The war in Ukraine has severely disrupted global food supplies, leading to a sharp rise in prices for staple crops like rice, wheat and barley. Many vulnerable countries that rely heavily on food imports are being hit particularly hard. Over 1.4 billion people live in highly exposed countries, mostly in Africa and Asia. They face elevated inflation, budgetary stress, and rising malnutrition levels as they struggle to protect their populations from skyrocketing food prices.

Meanwhile, trade restrictions imposed by countries trying to shore up domestic supplies are further exacerbating the global food crisis. The World Bank estimates that over 800 million people worldwide already suffer from high levels of malnutrition or undernourishment. Urgent action is needed to prevent the situation from deteriorating further. The World Bank has committed \$45 billion to tackle the crisis, including measures to expand social protection, boost agricultural productivity, and facilitate trade [2]. However, long-term solutions require transforming food systems to be more sustainable, resilient, and equitable.

Because of rising food prices, falling household incomes, and rising unemployment, economic recessions can leave communities more vulnerable. Due to its ability to diversify farmers' crop rotation and decrease reliance on a single crop, millets have the potential to play a major role in ensuring food security during difficult times. Because this diversification ensures alternate sources of food if one crop fails and it could assist boost food security [3].

Millets are highly climate-resilient crops that can thrive in arid and semi-arid regions with minimal water and input requirements, making them wellsuited to withstand the effects of climate change. Millets, being highly nutritious, may help address the issue of malnutrition prevalent in many regions of the world.

Global millet production is estimated to be 54.75 million tonnes in 2022-23, up from 51.1 million tonnes in the previous year. India has seen a steady increase in the production of both major cereals and millets in recent years. The grains can withstand temperatures as high as  $26^{\circ}$ C to 42°C with 70% higher water use efficiency than rice. Since millets can withstand high temperatures, they are a great option for tropical nations. Millets are "usually the last crops standing in droughts," according to the International Crops Research Institute for the Semi-arid Tropics [4]. However, the country faces the challenge of addressing the growing "cereal gap" and leveraging the potential of climate-resilient and nutritious crops like millets to enhance food security and sustainability.

## **2. PEARL MILLET**

Pearl millet, also known as bajra, is one of the most widely grown and important millets globally. Pearl millet is highly nutritious, containing high levels of protein, fiber, minerals like iron, zinc, and calcium, and antioxidants. Compared to other cereals like rice and wheat, shifting to pearl millet and sorghum can increase protein (46%), iron (353%), and zinc (82%) production which makes it highly beneficial for addressing micronutrient deficiencies. Pearl millet is an efficient gluten-free grain and it is highly recommended for people who have celiac disease or gluten intoleranc. It is advantageous for managing diabetes because it is low in fat and has a low glycemic index.

Pearl millet is highly resistant to abiotic stresses like drought, heat, and low soil fertility. It can thrive in harsh climatic conditions where other cereals may fail. Pearl millet cultivation is more resilient to the impacts of climate change compared to other cereals and it shows considerable tolerance to various biotic stresses through natural resilience and tolerance mechanism. Its small grains, nutritious composition, and stress resistance make it a promising crop for the future. In the Indo-Gangetic Plains, switching from rice to pearl millet and sorghum during the Kharif season can reduce water use by 32% [5] This is crucial for sustainable water conservation in water-stressed regions.

India is the world's largest producer of pearl millet, accounting for 44% of global millet production. The area under cultivation of Pearl millet in India for the 2023-24 crop year is 7.41 million hectares with the production of around 10.3 million tonnes and productivity around 1391 kg per hectare. The major pearl millet producing

states in India are Rajasthan (44% of production), Uttar Pradesh (15%), Haryana (11.4%), Maharashtra (10.8%), and Gujarat (10.5%) [6]. While pearl millet consumption has declined in recent decades, it is now gaining importance due to its climate resilient nature, nutritional status and use as food and feed products.

#### **3. CLIMATE RESILIENCE OF PEARL MILLET**

Pearl millet can withstand harsh growth circumstances like drought, low soil fertility, and high temperatures and it is usually grown as a rainfed crop with little input. It can produce superior yields in stressed environments where other cereals like wheat and rice fail to provide economic returns. Its capacity to endure higher temperatures and thrive in drought-prone regions, makes it a climate-resilient crop capable of mitigating the adverse impacts of climate change [7].

## **3.1 Tolerance to Abiotic Stress**

Abiotic stresses negatively impact the growth and yield potential of all crops, including pearl millet. Therefore, identifying and utilizing genetic variations for abiotic stress tolerance is crucial for improving its adaptation to these stresses. Flowering time and photoperiodic sensitivity significantly impact the yield and yield stability of pearl millet. Pearl millet typically exhibits photoperiod sensitivity, with most landraces flowering under short-day conditions [8]. This trait allows for flexible sowing dates, ensuring that flowering and grain maturity coincide with the end of the growing season. Research indicates that pearl millet has adaptive mechanisms (morphological- root system, leaf structure, leaf angle; physiological- osmotic adjustment, stomatal regulation, heat shock proteins; anatomical- cuticle thickness, sunken stomata; biochemical- antioxidants defence, secondary metabolites) demonstrating its adaptability to varying environmental conditions [9].

Pearl millet has a deep and extensive root system that allows it to access water from deeper soil layers, which is crucial for surviving prolonged periods of drought. These root features are linked to many traits associated with abiotic stress tolerance, including crop performance, water and nutrient use efficiency. Pearl millet is largely drought-tolerant because of its capacity to retain high leaf water status and increase total root length in the face of soil drying [10]. During water scarcity, nitrogen uptake decreases because the plant's demand for nitrogen diminishes as its growth rate slows. Additionally, nitrogen absorption by roots relies on the presence of water, which transports solutes to the soil-root interface [11]. Pearl millet's capability to maintain sustained water uptake through its fast-growing roots enhances its water and nutrient use efficiency. It had been revealed according to rhizotron and microcomputed tomography (micro CT) phenotyping techniques that early-stage root development in pearl millet, characterized by rapid primary root growth and distinct lateral roots, is crucial for early-stage drought stress tolerance [12]. Pearl millet is a C4 grass that has evolved naturally to use water efficiently in high light conditions through the usage of the NADP-dependent malic enzyme pathway [13]. By separating carbon fixation in the bundle sheath cells from the light reactions of photosynthesis in the mesophyll cells, this mechanism lessens the rivalry between  $o$ xygen and  $CO<sub>2</sub>$  molecules for the Rubisco enzyme. As a result, compared to C3 grasses like wheat or rice, this minimizes the need for extended stomatal opening, which boosts water usage efficiency.

Numerous studies on antioxidant gene expression profiling have been conducted in pearl millet under drought conditions. Genes encoding drought tolerance were significantly upregulated in drought-tolerant genotypes treated with polyethylene glycol to mimic drought stress at both early and late seedling stages. Such genes are ascorbate peroxidase (APX), glutamyl-tRNA reductase (GlutR), and superoxide dismutase (SOD) [14]. This increased gene expression in tolerant genotypes indicates their role in scavenging reactive oxygen species (ROS) during drought stress [15]. A transcriptomics analysis further supported these findings, revealing significant up-regulation of differentially expressed genes (DEGs) encoding ROS-scavenging enzymes like SOD, APX, and glutathione peroxidase (GPX) during the vegetative stage under drought conditions [16].

Another method for drought resistance involves the presence of a waxy outer layer [17]. In the pearl millet genome assembly, which includes approximately 38,579 genes, there is a significant abundance of genes related to the biosynthesis of cutin, flavonoids, suberin, and wax [18].Genes differentially expressed in tolerant genotypes were primarily linked to

secondary metabolite pathways like mevalonate, shikimate, alkaloids, phenols, flavonoids, lignin, and wax biosynthesis, as well as stress-related phytohormones such as ABA, ethylene, gibberellic acid, jasmonic acid, and salicylic acid [19].

During flowering, pearl millet can withstand temperatures as high as  $26^{\circ}$ C to  $42^{\circ}$ C, which sets it apart from other main food crops like rice, wheat, and maize. Pearl millet has greater tolerance to high temperature stress compared to maize [20]. It responds to heat stress by producing various proteins, notably heat shock proteins (HSPs), which play crucial roles in stress tolerance. These proteins aid in stress signal transduction and gene activation, with HSPs/chaperones facilitating heat shock factor (HSF) activity and defense mechanisms against reactive oxygen species (ROS) that arise from heat stress, thus preventing protein misfolding. Genes encoding calnexin and calreticulin, which process misfolded peptide chains in response to heat stress, were upregulated and differentially expressed, underscoring the ER system's critical role in heat resistance [21].

Salinity stress significantly reduces crop productivity and yield potential. Factors such as low precipitation, irrigation using saline water, and inadequate irrigation practices contribute to this stress. Proline, total soluble protein, and epicuticular wax content are among the several physiological and biochemical reactions that pearl millet cultivars that have acclimated to saline conditions show when salinity levels rise. [22].

Transcriptomic studies in pearl millet have identified several salinity stress-responsive genes including PgDHN, PgDREB2A, PgVDAC, and PgNHX1 [23]. Identified salinity-tolerant pearl millet lines (ICMB 02111, ICMB 94555, ICMB 95333, ICMB 00888, ICMB 01222, ICMP 451, IP 3732, IP 3757, ICMV 93753, and ICMV 94474) should be incorporated into breeding programs to develop locally adapted cultivars with enhanced salinity tolerance [14].

#### **3.2 Tolerance to Biotic Stress**

Crops that are subjected to abiotic stress are also more vulnerable to weeds, infections, and other insects, which greatly reduces crop yields. Occurrence of infection and disease are facilitated by moderate temperatures (20–30°C) and high relative humidity (85–90%). A number of organisms, including viruses, bacteria, fungus, insects, pests, birds, and weeds are the biotic stressors that can seriously hinder worldwide agricultural productivity. Pearl millet, like other cereals, is vulnerable to these biotic stresses. However, due to its predominant cultivation in dry climates, millets generally face lower risks of biotic stress compared to other crops. Various fungal infections such as downy mildew (*Sclerospora graminicola*), blast (*Magnaporthe grisea*), rust (*Puccinia substriata* var. indica), ergot (*Claviceps fusiformis*), and smut (*Tolyposporium penicillariae*) are particularly detrimental to the growth and yield of pearl millet compared to other pathogens [24].

Downy mildew, caused by *Sclerospora graminicola*, is a significant disease of pearl millet, originally traced to Africa. It poses a major biotic challenge in India and West Africa, leading to pearl millet grain yield losses estimated between 10% to 80% [25]. Blast disease, caused by *Magnaporthe grisea*, has affected nearly all pearl millet-growing states in India since 1970. Despite various control methods such as seed sanitation and chemical treatments against seed, soil, and airborne pathogens, emphasis has primarily been placed on developing host-plant resistance due to its effectiveness. Major insect pests of pearl millet include shoot fly (*Atherigona approximata*) (yield loss- 40%), grey weevil (*Myllocerus* spp.) (yield loss- 30%), and white grub (*Holotrichia consanguinea*) (yield loss-50%). Other minor pests causing economic damage include stem borers, hairy caterpillars, cutworms, chaffer beetles, blister beetles, and grasshoppers. Presence of weeds throughout the season can result in 43.8% decrease in pearl millet grain yield. Common weeds in pearl millet include *Trianthema portulacastrum, Echinochloa colona, Digeria arvensis* and *Cyperus rotundus*. Since most of India's pearl millet-growing regions have lower rates of insect pests, official breeding efforts that expressly target insect resistance are not yet well-established. Most people agree that the best way to manage diseases in different crops is to utilize resistant cultivars. Key tactics used in resistance breeding against biotic stresses include efficient screening techniques, the use of a variety of germplasm, the identification of resistant sources, an understanding of the genetic basis of resistance, research on virulence variability, the application of efficient resistance breeding techniques, and monitoring cultivar performance in field settings. Researchers have successfully identified stable sources of germplasm in pearl millet that exhibit

resistance to diseases such as downy mildew, blast, rust, smut, and ergot, some of which have been incorporated into disease resistance breeding programs. Mapping, investigating, and implementing efficient blast resistance tactics can be accomplished by leveraging the additional genetic and genomic resources that are currently available [26]. Furthermore, wild relatives of pearl millet germplasm present opportunities for strengthening pearl millet resistance to biotic stress and for germplasm enhancement [24]. Various resistant genotypes for downy mildew, blast, rust, smut, ergot, and other biotic stresses in pearl millet, preserved at ICRISAT and NBPGR had been catalogued [27].

Transcriptomic analysis using next-generation sequencing tools in pearl millet elucidated that resistant genotypes activate genes in the phenylpropanoid pathway, induce hypersensitive responses, and enhance systemic acquired resistance as effective defense mechanisms against downy mildew infection [28]. Moreover, various advanced genomic and biotechnological tools have been applied to identify resistant sources, quantitative trait loci, and genes for different biotic stresses [14]. 305 accessions of *Pennisetum violaceum*, a wild relative of pearl millet, under greenhouse conditions against multiple pathotype isolates of *Magnaporthe grisea* and a local isolate of *Pennisetum substriata* var. indica were screened to identify diverse sources of resistance against blast and rust diseases [24]. Integrated approaches encompassing stress biology, genomics, and bioinformatics are pivotal in developing crops resilient to stress.

#### **4. NUTRITIONAL AND ANTI-NUTRITIONAL PERSPECTIVES OF PEARL MILLET**

#### **4.1 Nutritional Perspectives**

Pearl millet plays a crucial role in nourishing the poverty-stricken populations due to its high palatability and rich nutritional profile [29]. It includes a high content of dietary fiber, and minerals such as calcium, iron, potassium, zinc, and magnesium, as well as B vitamins. It also serves as an excellent source of well-balanced protein, particularly abundant in threonine, although it lacks lysine and has lower leucine levels compared to sorghum. Notably, pearl millet contains ample tryptophan levels, surpassing other cereal crops. Its nutritional value stands out among millet crops, boasting high concentrations of calcium, iron, zinc, lipids, and high-quality proteins, making it a superior choice for addressing malnutrition and food security challenges in resource-constrained regions (Table 2).

Pearl millet is also low in glycemic index and gluten, which makes it a good food for people with gluten sensitivity and for controlling blood sugar levels. However, the bioavailability of these nutrients may be impacted by the presence of anti-nutritional elements such tannins and phytic acid [30].

# **4.2 Health Enhancing Properties**

The inclusion of pearl millet in the diet not only enhances nutritional security but also offers potential health benefits, making it a valuable addition to combat various health issues and promote overall well-being.

#### **1. Hypoglycemic properties**

Pearl millet exhibits significant hypoglycemic properties due to its bioactive peptides, phenolics, and phytochemicals. Proteolytic enzymes (lalcalase, bromelain, and chymotrypsin) generate pearl millet protein hydrolysates with potent anti-diabetic potential, inhibiting α-amylase and dipeptidyl peptidase-IV and has lesser glycemic index than many cereal grains. Additionally, pearl millet flour blended with sweet detar flour or sodium carboxymethyl cellulose shows enhanced α-amylase and αglucosidase inhibitory activities, crucial for managing type 2 diabetes [31]. Phenolics in pearl millet play a vital role in inhibiting carbohydratedigesting enzymes and regulating glucose uptake, showcasing its anti-hyperglycemic potential [32].

#### **2. Anticancer properties**

Pearl millet has been investigated for its anticancer properties. Studies have shown that polyphenols extracted from pearl millet exhibit cytotoxic effects against HepG2 hepatic cancer cell lines, suggesting it could be a natural source of anticancer agents. Additionally, cysteine protease inhibitor (CPI) in pearl millet has demonstrated anti-fungal activity, indicating potential applications in disease prevention, including cancer [33]. Furthermore, pearl millet contains antioxidants and certain compounds (ellagic acid, gallic acid, and quercetin) which

have shown anticancer effects by inhibiting matrix metalloproteinases (MMPs) and protein kinase C (PKC) [34]. Bioactive components like ferulic acid and p-coumaric acid have been found to enhance the sensitivity of drug-resistant colorectal cancer cells to chemotherapy drugs like oxaliplatin by modulating ganglioside metabolism and reducing multidrug resistance protein 1 (MDR1) expression [35]. Additionally, CPI has exhibited anti-fungal and anti-feedent activities in pearl millet, suggesting its potential in developing transgenic plants resistant to pathogens and pests, offering a novel approach to cancer treatment through genetic modification [36].

#### **3. Probiotic properties**

Fermentation processes involving different microorganism combinations led to increased mineral content (calcium and iron) as observed in various studies Fermented pearl millet showed higher levels of total phenols and oligopeptides. along with increased resistant starch content and prebiotic activity, particularly when fermented with *Saccharomyces cerevisiae* plus *Campanilactobacillus paralimentarius* [37].

## **4.3 Biofortification of Pearl Millet**

Biofortification is the process of increasing the concentration of essential vitamins and minerals in food crops through genetic improvement or<br>adronomic practices. Scientists have agronomic practices. Scientists concentrated on boosting the bioavailability of important micronutrients like iron and zinc, which are frequently lacking in people's diet. The process of biofortification of pearl millet involves various techniques, including breeding (selective breeding, hybrid development, genome mapping, genetic engineering), agronomic practices (crop rotation, soil and fertilizer management), and post-harvest processing (dehulling, milling, thermal processing, extrusion, soaking and germination) [30]. Recent developments in the field of biofortification have led to the creation of iron- and zinc-enriched pearl millet varieties (Table 3), which have the potential to address issues of micronutrient deficiency in vulnerable populations [38].

# **4.4 Value Added Products of Pearl Millet**

In the Indian subcontinent, pearl millet is typically consumed in the form of flattened bread or chapathi. Conversely, in the African subcontinent, fermented breads are more

commonly used instead of flatbreads. Fura, a perishable food shaped into balls, is prepared by cooking a blend of fermented and non-fermented pearl millet flour with spices. This food is popularly consumed across Nigeria, often paired with yogurt ('nono') or mixed with water to make porridge, varying by region [40]. Porridges are breakfast cereals that can be consumed as either a thin or thick food, depending on their consistency. Dalia, a popular cereal-milk-based porridge in India, exemplifies this dish. The instant dalia mix contains 30% grain mix (40%

pearl millet, 50% sorghum, and 10% maize), skim milk powder (40%) and sugar (30%). They found that this mix had superior protein content and lower fatty acid content. Additionally, the product maintained its quality for over 71 weeks when stored at 10°C [41]. As consumers' awareness of health issues grows, the frozen dessert sector is currently looking for dairy fat substitutes. At 1% and 2% concentrations, octenyl succinyl anhydride esterified pearl millet starch has been found to be a useful fat substitute in ice creams [42].





#### **Table 2. General nutritional composition of Pearl Millet**



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*Source: USDA Nutrient Database [http://ndb.nal.usda.gov/ndb/search/list].*

In addition to being used in salted products, pearl millet grains are also utilized in making sweets. For example, small, sweet balls known as Ladoo and Dakuwa, made from roasted pearl millet grain flours, are popular in India and Nigeria, respectively. These sweets could be enhanced by incorporating ingredients such as popped pearl millet grain and malted flour for nutritional benefits [43]. Pearl millet flour also holds promise for creating various globally popular products, including ready-to-eat snacks, weaning foods and non-dairy fermented beverages. Furthermore, it can serve as an alternative to wheat flour in a variety of food preparations such as biscuits, pastas, whole meal breads, and kibbeh.

## **4.5 Antinutritional Factors**

Pearl millet contains antinutritional factors such as phytic acid, tannins, and polyphenols, which can hinder the absorption of essential minerals like iron and zinc [44]. These antinutrients reduce the bioavailability of minerals in millets, impacting their overall nutritional value. Traditional processing methods, including roasting, blanching, and malting, have been shown to significantly decrease the levels of phytic acid in

millets, thereby enhancing nutrient absorption [45]. Additionally, pearl millet germplasm exhibits variability in the levels of phytic acid and goitrogenic compounds, highlighting the potential for breeding programs to develop new varieties with improved nutritional quality and reduced antinutrient content [46]. By understanding and addressing these antinutritional factors, the nutritional value of pearl millet can be enhanced, making it a more beneficial food source for populations in developing countries where deficiencies in iron and zinc are prevalent.

# **5. WAY FORWARD**

Improving pearl millet for climate resilience and nutritional value involves a multi-faceted approach that includes breeding for desirable traits, effective soil and pest management, and innovative processing techniques to enhance nutrient availability. Development of resistant hybrids/varieties resistant/tolerant. Shift in focus of breeding from productivity improvement to the identification of stress specific traits. Development of efficient screening protocols and control measures against different diseases and pests of pearl millet. Biofortification in pearl millet for minor nutrients. Prolonged shelf life of pearl millet flour and overcome rancidity. This not only supports food security but also addresses nutritional deficiencies in vulnerable populations.



#### **Table 3. List of biofortified pearl millet varieties & hybrids**

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Name of the hybrid/Variety	Grain yield (Kg/ha)	<b>Micronutrients</b> (ppm)		<b>Institute</b> developed	<b>Special Character</b>
& Year of release		Fe	Zn.		
HHB 67 Imp 2 (1990)	2000	55	40	CCSHAU, Hisar, India	Resistant to downy mildew
<b>BHB-1202</b>	1776	47	42	ICAR-AICRP- PM, SKRAU, Bikaner, India	highly resistant to downy mildew, blast and major pests
			ГЗ9 і		

#### **6. CONCLUSION**

Pearl millet emerges not only as a resilient crop in the face of climate change but also as a vital contributor to global food security and nutrition. Its ability to thrive in harsh environments, characterized by heat and drought, makes it a dependable option for regions susceptible to erratic weather patterns. Furthermore, its nutritional profile, rich in essential minerals, proteins, and gluten-free properties, positions it as a valuable resource in combating malnutrition and addressing dietary deficiencies worldwide.

As we confront the challenges of a changing climate and a growing global population, promoting the cultivation and consumption of pearl millet offers a sustainable solution. Continued research and investment in pearl millet production not only bolster food security but also contribute to the resilience of agricultural systems in the face of increasingly unpredictable environmental conditions. Embracing pearl millet represents a forward-thinking approach to ensuring food security and promoting nutritional diversity on a global scale.

#### **DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

#### **COMPETING INTERESTS**

Authors have declared that no competing interests exist

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