

Unleashing the potential of millets: a comprehensive review of its nutritional, therapeutic, and genomic attributes

Biju Vadakkemukadiyil Chellappan,¹ Peramaiyan Rajendran^{1,2}

¹Department of Biological Sciences, College of Science, King Faisal University, Al-Ahsa, Saudi Arabia; ²COMMANd, Department of Biochemistry, Saveetha Dental College & Hospitals, Saveetha Institute of Medical and Technical Sciences, Velappanchavadi, Chennai, Tamil Nadu, India

Abstract

Millets are cereal grains whose farming dates back thousands of years and have been farmed and consumed by a wide variety of cultures around the world. In recent times, there has been a growing interest in millets due to their medicinal characteristics and nutritional advantages. Millets have a substantial nutritional content and

can provide a wide range of beneficial health effects. These foods have a relatively low glycemic index in addition to their high levels of dietary fiber, proteins, vitamins, and minerals. In this review, the most recent information regarding the potential effects of millets on the management of diabetes, the health of the heart, antioxidant activity, anti-cancer capacities, and other therapeutic benefits is investigated. In addition, the report provides an in-depth analysis of the current genome resources that are associated with millets, as well as a summary of the key genetic discoveries that have been made. The report also emphasizes the need for further research to maximize the potential of millets through the utilization of genetic resources and breeding techniques to develop high-nutrient-rich and climate-resilient varieties.

Correspondence: Peramaiyan Rajendran, Department of Biological Sciences, College of Science, King Faisal University, P.O. Box 420, Al-Ahsa 31982, Saudi Arabia.
Tel.: +966.135899543.
E-mail: prajendran@kfu.edu.sa

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Introduction

Millets encompass a wide array of small-seeded grains that fall within the taxonomic classification of the Poaceae family. The cultivation and consumption of these ancient grains may be traced back to many civilizations spanning thousands of years, with their beginnings dating back to the Neolithic era.¹ Millets are renowned for their robustness, capacity to thrive in many agro-climatic environments, and remarkable nutritional profile, rendering them a vital means of sustenance for populations throughout various regions of the globe.^{2,3} The most prominent types of millets include pearl (*Pennisetum glaucum* (L.) R.Br.), finger (*Eleusine coracana* (L.) Gaertn.), foxtail (*Setaria italica* (L.) P.Beauv.), proso (*Panicum miliaceum* L.), barnyard (*Echinochloa crus-galli* (L.) P.Beauv.), sorghum (*Sorghum bicolor* (L.) Moench), kodo (*Paspalum scrobiculatum* L.), browntop (*Urochloa ramosa* (L.) T.Q.Nguyen), and little millet (*Panicum sumatrense* Roth) (Figure 1). Figure 2 showed the evolutionary relationships and ortholog genes shared by millet varieties. Millets have been cultivated across Asia, Africa, and Europe for millennia, adapting to a wide range of climatic and soil conditions.⁴ The capacity of these plants to thrive with limited water demands and reduced reliance on chemical inputs makes a significant contribution to the implementation of sustainable farming methods. Millets are recognized for their minimal carbon footprint, rendering them environmentally benign and robust to climate change.⁵

The demand for millets has dramatically expanded during the last few years. The size of the millets market was estimated at USD 12.33 billion in 2022. From 2023 to 2028, the global millet market is anticipated to increase at a rate of 4.60%, reaching about USD 16.27 billion in 2028. India is the topmost producer of millets, followed by China and Niger. With a share of roughly 30%, the United States takes the lead in exports. Indonesia, Iran, Germany, Belgium, and South Korea import 50% of the world's millets. Millets are

known as “nutri-cereals” because of their exceptional nutritional content. They are expected to play a significant role in addressing malnutrition and nutrient deficiencies, particularly in areas with restricted access to a variety of dietary sources. As highly nutritious crops with significant drought tolerance, millets play a vital role in ensuring food security in areas subject to climatic change and natural disasters. Their resilience to adverse conditions helps farmers maintain a stable food supply even in challenging times, thus reducing the impact of food crises.

This article presents an up-to-date, complete overview of the therapeutical and genetic features of millets, as well as a discussion on future research that further warrants more investigation.

Nutritional composition of millets

Millets are distinguished by their remarkable nutritional content. The grains provide a variety of important macronutrients, including carbohydrates, proteins, and lipids. Moreover, they are abundant in dietary fiber, minerals, and vitamins.

The carbohydrate content in millets varies slightly depending on the variety, but it typically ranges from 60% to 79% of the grain's dry weight (Table 1).^{6,7} The carbohydrate composition of millets primarily consists of starch, which varies from 32 to 83% and is composed



Figure 1. Seeds of nine types of millets.

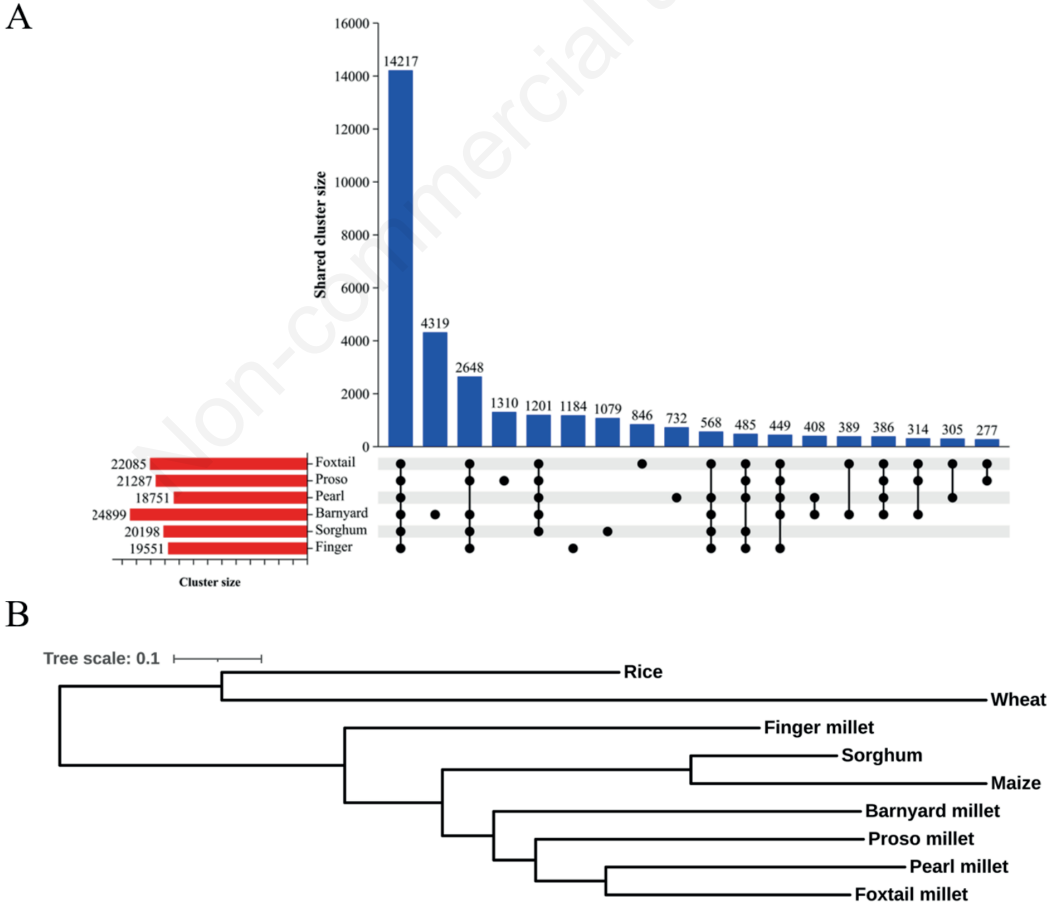


Figure 2. Shared orthologue genes and phylogeny of millets. A. Orthologue gene clusters in millets. Blue bars represent the number of clusters shared by millets, represented by numbers shown above the bar. Line and dot connections between species that share orthologs. B. Phylogenetic relationship among millets. The red bar represents the gene cluster size in each millet species.

of amylopectin (70-80%) and amylose (20-30%).^{7,8} Finger millet contains the highest concentration of carbohydrates, ranging from 65 to 83.3% of the dry grain weight.⁹ The finger millet's carbohydrate composition includes starch (65%), pentosans (6.2–7.2%), cellulose (1.4–1.8%), and lignins (0.04–0.6%).^{7,9} Studies have shown that the carbohydrate content in different pearl millet genotypes varies between 56.5 and 75.6%.^{9,10} Pearl millet grains have a sugar content of 1.2–2.6%, an amylose content of 21.9–28.8%, and provide around 363 Kcal of energy per 100 g of seeds.¹¹ In foxtail millet varieties, the carbohydrate content varies from 60 to 74.6%, and it is mostly composed of amylose (17%) and amylopectin (82.5%).^{9,12,13} The carbohydrate content of other millets is as follows: browntop millet (51.5–71.8%), proso millet (51.2–77.1%), barnyard millet (51.5–71.8%), kodo millet (59.2–66.1%), little millet (65.5%) and sorghum (32.1–72.1%).^{9,14–17} Dietary fiber constitutes another important fraction of carbohydrate composition in millets, particularly whole grains, which are rich in both soluble and insoluble fiber.⁷ When comparing several millet types, it was found that proso millet varieties exhibited the highest quantity of dietary fiber (Table 1). On average, proso millet contained 22.9 g of fiber per 100 g of dry weight, with a maximum of 36.3 g per 100 g of dry weight.¹⁸ Pearl millet had a dietary fiber content of 20.4 g per 100 g of dry weight, finger millet 18.6 g per 100 g of dry weight, barnyard millet 16.3 g per 100 g of dry weight, and sorghum 10 g per 100 g of dry weight.^{8,9,19,20} Foxtail millet and browntop millet contained 8 g of dietary fiber per 100 g of dry weight (Table 1).^{9,13,14} The content of little millet was 7.1 g per 100 g of dry weight, while kodo millet contained 6.3 g per 100 g of dry weight (Table 1).^{9,17–21}

The protein content of millet grains is comparable to or higher than that of other cereals such as wheat, rice, and maize grains.^{22,23} The main protein components found in millet grains include albumins, globulins, cross-linked prolamins, and glutelins.^{24,25} The highest protein content is recorded in pearl millet (20.08 g/100 g dry weight), followed by browntop millet (19.33 g/100 g dry weight), foxtail millet (18.5 g/100 g dry weight), finger millet (16.9 g/100 g dry weight), and proso millet (16.9 g/100 g dry weight), which is high compared to wheat (10.59 g/100 g dry weight) and rice (9.16 g/100 g dry weight) (Table 1).^{7,9,22,23,26} Other millets, like sorghum, barnyard millet, kodo millet, and little millet also contain protein amounts comparable to those of wheat and rice.^{9,15,16,24,27,28} Millets are nutrient-dense grains that contain a variety of essential micronutrients. The specific micronutrient content can vary between different types of millets, but in general, millets are known to provide a range of important minerals and trace elements such as iron, magnesium, potassium, phosphorus, zinc, calcium, and others (Table 1).¹⁰

For instance, finger millet is a good source of calcium (1400 mg/100 g) and magnesium (900 mg/100 g) (Table 1). Similarly, millets are rich sources of vitamin B complex and vitamin E. For example, foxtail and barnyard millets are rich in niacin (vitamin B3) and thiamine (vitamin B1) compared to wheat and rice.²⁹ The nutrient-rich nature of millets makes them a valuable food source, particularly for individuals with specific dietary needs or those seeking to improve their nutritional intake.

Antinutrients in millets and their mitigation strategies

Although millets are rich in nutrients such as carbohydrates, proteins, lipids, and crude fiber, their consumption may be limited by the presence of anti-nutritional factors (ANFs).^{30,31} Anti-nutritional factors are the compounds that bind to the nutrients present in food and make them less available for absorption by the human body.³² The presence of ANFs in millets can have significant health implications, including impaired mineral absorption, reduced protein and carbohydrate digestibility, potentially affecting growth and development, gastrointestinal discomfort and malabsorption issues, and an increased risk of kidney stone formation.^{32,33} Various antinutritional substances, such as phytates, tannins, alkaloids, lectins, and protease inhibitors, have been detected in cereal grains. However, tannins and phytates are the most significant antinutritional components in millet grains. Phytates, or phytic acid, are naturally occurring phosphorus-containing compounds found in the bran and outer layers of millets. They are negatively charged structures, due to which they attract positively charged substances like minerals such as calcium, iron, zinc, and magnesium and form insoluble complexes, thus inhibiting their absorption in the gut.^{33,34} Also, phytic acid reacts indirectly with the negatively charged group of proteins, mediated by positively charged mineral ions, which make proteins undigestible to some extent.³³ Several studies have highlighted the negative impact of phytates on mineral bioavailability and their potential contribution to mineral deficiencies. The millets were found to have a phytic acid level ranging from 317 to 1,640 mg/100 g.³⁵ Sorghum had the lowest phytic acid content, while browntop millet had the highest (Table 2).^{30,35–37} Tannins are polyphenolic chemicals found in the seed coat and pericarp of millets. They exhibit antioxidant capabilities, while also having the capacity to attach to proteins, carbohydrates, and minerals, decreasing their digestion and bioavailability.³³ Millets that are high in tannins can cause gastrointestinal pain and hinder the absorption of essential trace elements and nutrients, especially iron and proteins.^{30,33} According to recent research, sorghum has the

Table 1. Macro and micronutrients in millets.

Millet type	Macronutrients g/100g grain (dry weight)				Micronutrients mg/100g grain (dry weight)					References
	Carbohydrates	Fat	Proteins	Dietary fibres	P	Fe	Mg	Ca	Zn	
Pearl	56-75.6	4.1-7.4	9.4-20.8	2.5-20.4	570	13.5	240	73.7	9.4	(9,10,23,103-105)
Finger	65-83.3	1.2-2.2	5.8-16.8	15-22	210	14.7	900	1400	6.4	(7-9,106)
Foxtail	60-74.6	2.9-4.1	6.2-18.5	6.7-8	290	16.2	130	28.9	11.4	(9,13,107,108)
Browntop	58-71.3	1.9	8.9-19.3	8	276	15.3	NA	33	2.8	(9,14,26)
Proso	51.2-77.1	3.1-4.9	10.8-16.9	11-36.3	101	7.32	120	235.4	4.7	(9,18,22,109)
Barnyard	51.5-71.87	3.5-4.6	11.2-12.7	8.1-16.3	280	18.6	82	27.1	4.8	(9,15,19,110)
Kodo	59.2-66.19	2.5-3.6	7.0-9.3	6.3	378	24.7	1.4	23.5	6.5	(9,17,24,28,111)
Little	65.55	2.5-3.9	7.2-14.6	7.7	130	23.4	23.4	8	11	(9,16,21,112)
Sorghum	32.1-72.1	1.2-3.7	7.2-15.2	3.5-10.7	274	12.8	173.4	270	5.7	(9,20,27,113,114)

P, phosphorus; Fe, iron; Ca, calcium; Mg, magnesium; Zn, zinc.

highest tannin level at 601 mg/100 g, while browntop millet has the lowest tannin content at 2.12 mg/100 g.³⁸ Oxalic acid (oxalates) is an organic acid present in millets that can form insoluble complexes with calcium, leading to reduced calcium absorption and an increased risk of kidney stone formation in susceptible individuals.³⁶ Among the several types of millets, sorghum had the highest concentration of oxalic acid, whereas kodo millet had a lower level of 3.41 mg per 100 grams.³⁵⁻³⁷ Millets also include anti-nutrients such as trypsin inhibitors and amylase inhibitors, which are digestive enzyme inhibitors that hinder the breakdown of proteins and carbohydrates, respectively.^{30,36} The trypsin inhibitory activity of protease enzymes ranged from 73.11 to 789.2 IU/g, as indicated by the available data. Among these, browntop millet demonstrated the most inhibitory action, whereas barnyard millet displayed the lowest activity, as indicated in Table 2.³⁷

Several bioprocessing techniques offer promising avenues to reduce anti-nutrient levels in millets while preserving their nutritional integrity.^{30,39} These techniques include soaking, germination/sprouting, cooking, malting, and fermentation of the grains. Soaking is an easy way to reduce anti-nutrients in several millets.³⁹ Germination involves soaking millet grains in water to induce sprouting, leading to enzymatic activity that degrades anti-nutrients such as phytic acid and tannins. Several studies have demonstrated the effectiveness of germination in reducing anti-nutrient levels and improving the bioavailability of minerals in millets.^{40,41} Fermentation utilizes microorganisms such as lactic acid bacteria and yeast to degrade anti-nutrients through enzymatic activity.⁴² Fermentation not only reduces anti-nutrient levels but also enhances the sensory properties and digestibility of millet-based products.⁴³ Malting involves controlled germination and drying to produce malted millet. This process activates endogenous enzymes that degrade anti-nutrients while improving the nutritional quality and flavor profile of millets.^{44,45} Enzyme treatments utilize specific enzymes, such as phytase, to hydrolyze phytic acid, reducing its anti-nutrient effects. Enzyme treatments offer precise control over the bioprocessing of millets, resulting in superior nutritional outcomes.^{46,47}

Therapeutic properties of millets

Millets have gained significant attention in recent years due to their exceptional therapeutic properties and potential health benefits. These ancient grains, packed with essential nutrients, offer a wide range of advantages that can positively impact human health. Some of the key therapeutic properties of millets are discussed in the following subchapters (see below).

Diabetes management

Diabetes is a chronic metabolic disease and a serious health problem, with the number of people living with diabetes expected to increase to 642 million by 2040.⁴⁸ Type 2 diabetes (T2DM), which is caused by insulin secretion reduction and pancreatic β -cell dysfunction, accounts for 90% of diabetes and is one of the leading causes of death.⁴⁹ Although chemical drugs are available to treat T2DM, many patients have experienced the side effects of these drugs. Therefore, the demand for healthy foods to alleviate and improve T2DM is increasing. Millets are known for their low Glycemic Index (GI), which is a measure of how quickly carbohydrates in a food raise blood glucose levels after consumption. Foods with a low GI value release glucose into the bloodstream gradually, providing a more sustained and steady supply of energy. This property makes millets particularly beneficial for blood glucose regulation, especially for individuals with diabetes or those looking to manage their blood sugar levels. Recent studies showed that the consumption of whole foxtail millet and its components can improve glucose metabolism.^{50,51} In a recent study, Wang *et al.* showed that the treatment of lipid extract from foxtail millet mitigates glucose metabolism disorders and lipid accumulation in high-fat diet/streptozotocin (HFD/STZ)-induced diabetic mice.⁵² In a separate study, Wang *et al.* demonstrated the potential hypoglycemic effects of heat-treated starch and proteins derived from foxtail millet (*Setaria italica*) on mice with type 2 diabetes.⁵³ Several studies have demonstrated that the inclusion of finger millet in the diet is correlated with reduced blood glucose levels in individuals diagnosed with T2DM when compared to a diet primarily consisting of rice.^{54,55} In a recent study, Mudgil *et al.* demonstrated the antidiabetic properties of pearl millet protein hydrolysates by inhibiting the function of some antidiabetic enzymatic markers such as α -amylase and α -glucosidase.⁵⁶ The antidiabetic properties of proso millet were investigated recently by Deng *et al.*, who demonstrated that proso millet whole grain suppressed the expression of gluconeogenesis-related genes such as *G6Pase*, *Pepck*, *Foxo1*, and *Pgc-1 α* . The authors also demonstrated that the treatment with proso millet improved phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) signaling and the miRNA expression profile in the liver of T2DM mice, thus alleviating symptoms such as liver and kidney injury, abnormal glucolipid metabolism, and insulin resistance.⁵⁷ Anis *et al.* in 2020 demonstrated that phenolics of barnyard millet can inhibit protein glycoxidation and advanced glycation end-product formation associated with diabetes, suggesting the potential use of barnyard to manage diabetes.⁵⁸ Although the above studies have shown the

Table 2. Anti-nutrients in millets.

Millet types	Phytic acid (mg/100g)	Tannin (mg/100g)	Total phenols (mg/100 g)	Oxalic acid (mg/100g)	Trypsin inhibitory activity (IU/g)	References
Sorghum	317.7	601	333.58	112	357	(30,35)
Finger	569	301	136.4	39.38	176.93	(30,115)
Pearl	477	232	415	26.50	193.76	(30,36)
Kodo	1268	124.7	493	3.41	236.14	(36,116)
Little	633	15.7	133	6.87	110.26	(36)
Barnyard	676	35.5	270	20.65	73.11	(36)
Foxtail	973	48	245	11.19	182.34	(36,117,118)
Proso	720	21.8	375	8.54	119.88	(36,117,118)
Browntop	1640	2.12	173.5	4.12	789.2	(37,38)

potential use of millets in managing diabetes and controlling blood sugar levels, further research is required to fully understand the underlying mechanisms and the lasting effects.

Heart health

Millets can play a beneficial role in supporting heart health due to their various nutritional components and low glycemic index. Millets contain phytosterols, plant compounds structurally similar to cholesterol. Phytosterols can inhibit cholesterol absorption, contributing to reducing blood cholesterol levels and supporting heart health.⁵⁹ Major phytosterols in millets are campesterol, stigmasterol, and β -sitosterol, and the therapeutic properties of these compounds were demonstrated in several studies.^{60,61} In a recent study, Magalhães *et al.* showed that the consumption of germinated cooked pearl millet significantly reduced cholesterol levels in experimental rats, suggesting its potential use for a healthy diet.⁶² In another study, Liu *et al.* showed that the polyphenols in millet shells are effective in inhibiting the formation of macrophage-derived foam cells and also increasing high-density lipoprotein cholesterol (HDL-C).⁶³ Similarly, in another study, the anti-obesity, hypoglycemic, hypolipidemic, anti-inflammatory, and anti-steatotic properties of both pearl millet powder and ethanolic extract were demonstrated in obese rats fed a high-fat diet.⁶⁴

Antioxidant and anti-inflammatory properties

Millets are rich in polyphenolic compounds, which are secondary metabolites that occur naturally in plants and include tannins, flavonoids, and phenolic acids.³¹ Various polyphenols in millets are syringic acid, gallic acid, vanilic acid, 4-hydroxyl benzoic acid, and hydroxycinnamic acid derivatives such as caffeic acid, ferulic acid, sinapic acid, and others.³⁹ These polyphenolic chemicals act as powerful antioxidants, helping to neutralize harmful free radicals in the body and reducing oxidative stress. For example, ferulic acid is a strong antioxidant in most millets, as reported by Chadrsekhar and Shahidi in 2010.⁶⁵ Millets are a good source of vitamin E, a fat-soluble antioxidant that protects cell membranes from oxidative damage and works synergistically with other antioxidants to combat free radicals.⁶⁶ Previous studies have shown that millets contain alkylresorcinols, bioactive compounds with antioxidant and anti-inflammatory properties.^{67,68} Overall, this evidence showed that millets exhibit antioxidant and anti-inflammatory characteristics, which may enhance overall health and lower the risk of chronic conditions like cardiovascular diseases, diabetes, and some malignancies.

Anticancer properties

Several studies have shown that foxtail millet possesses a protective effect against various types of cancer.⁶⁹⁻⁷⁰ For example, in a recent study, Ren *et al.* showed that foxtail millet dietary fiber is effective against colon cancer by increasing the rate of apoptosis.⁷¹ Similarly, in another study, Zhang *et al.* demonstrated the potential inhibitory effect of polyphenols such as ferulic acid and p-coumaric acid from the inner shell of foxtail millet against breast cancer cells, possibly by promoting the accumulation of glycerophospholipids in breast cancer cells, which led to autophagic death.⁶⁹ The anti-breast cancer activity of foxtail millet is also supported by the recent study of Kuruburu *et al.*⁷⁰ Similarly, the anticancer properties of proso, barnyard, sorghum, and pearl millets were reported in various studies.^{31,72,73}

Other therapeutic properties

Recent evidence shows that millets possess diverse therapeutic properties other than those mentioned above. In a recent study, Wang *et al.* showed that heat-treated foxtail millet can mitigate the high-fat diet-induced non-alcoholic fatty liver disease by regulating gut microbiota composition.⁷⁴ Similarly, Shan *et al.* showed that millets bran protein hydrolysate possesses an anti-non-alcoholic fatty liver disease effect through the activation of peroxisome proliferator-activated receptor γ to restrain fatty acid uptake.⁷⁵ Another interesting study revealed that proso millet seed oil stimulates the β -catenin signaling pathway, promoting hair development in experimental rats, pointing to the possible application of this oil for the treatment of alopecia.⁷⁶ Many studies suggest that millets are suitable for individuals with celiac disease as they are gluten-free grains. Celiac disease is an autoimmune disorder in which the ingestion of gluten, a protein found in wheat, barley, and rye, triggers an immune response that damages the small intestine lining.⁷⁷ This damage can lead to various digestive and systemic symptoms. Previous studies have shown that millets are also good for osteoporosis as they are a good source of calcium.⁷

Genome resources of millets

Using high throughput and advanced sequencing technologies, several millet genomes were sequenced in the last decade. The elucidation of millet genome sequences has provided valuable insights into its genetic composition and the evolutionary patterns of key genes linked to agronomical characteristics, and paved the way for the use of sophisticated breeding methodologies. Furthermore, the application of comparative genomics has facilitated the examination of genetic variability within several millet species as well as the comparison of genetic distinctions among different millet varieties. The provided information holds significant value for breeding projects that are focused on the development of millet varieties with enhanced characteristics, including increased yield, resistance against pathogens, and higher nutritional quality. The genomes of the following millets have been sequenced so far (Table 3).

Pearl millet

The first draft genome of the pearl millet inbred Tift 23D2B1-P1-P5 cultivar genotype was sequenced and published in 2017.⁷⁸ In this sequencing effort, the authors used a combination of illumina, BAC clone, and PacBio sequencing data to generate the reference genome, which has a size of 1.8 gigabytes (Gb), which was assembled into 7 pseudomolecules (pearl millet haploid chromosome number is 7).⁷⁸ The genome contains more than 77% repetitive elements, dominated by retro-transposons. In total, 38,579 protein-coding genes were predicted, of which functions were assigned to 27,893 genes based on their homology with genes in the Swissport and Interproscan databases.^{79,80} The genome analysis revealed an expansion of 354 gene families, including those encoding suberin, cutin, and wax biosynthesis genes as well as those involved in the biosynthesis of secondary metabolites, such as the monoterpene and diterpene biosynthesis and terpenoid backbone. It was hypothesized that these genes might contribute to the heat and drought tolerance of pearl millet. The authors also identified 378 genes containing nucleotide binding sites (NBS), a domain conserved in all plant disease resistance genes (R genes), and observed that more than 51% of these genes were located in

two pseudomolecules (pg1 and pg4). Additionally, by resequencing 964 pearl millet lines, the authors also conducted genome-wide association research that resulted in the identification of 1,054 highly significant marker-trait associations (MTAs) for 15 variables, such as stover dry matter yield, grains per panicle, and grains per square meter. From this data set, Semalaiyappan *et al.* recently developed a 4K single nucleotide polymorphism (SNP) panel that was utilized to assess the genetic variation among 373 inbred lines of pearl millet.⁸¹ In a recent study, the pearl millet Tift 23D2B1-P1-P5 cultivar genotype was sequenced using Oxford Nanopore long reads technology, which has improved the overall quality of the reference genome by filling the gaps in the previous assembly and the number of genes mapped on the chromosome.⁸² In addition, a pan-genome of pearl millet was constructed by assembling the genomes of 10 representative accessions from eight major geographical regions and provided novel insights into the heat tolerance of pearl millet.⁸³

Finger millet

Finger millet (*Eleusine coracana*) is an allotetraploid species ($2n = 4x = 36$, AABB). The finger millet genome's estimated size is 1,593 megabytes (Mb) (84). So far, two genotypes have been sequenced to generate the genome assembly for finger millet, namely, ML-365 and PR202, respectively.^{85,86} The genotype ML-365 was sequenced using a combination of Illumina and Solid sequencing technology, which resulted in the generation of an assembly of size 1,196 Mb, which represented 82.1% of the estimated genome size of ML-365 (1,453 Mb).⁸⁵ The assembly was highly fragmented, with 525,759 scaffolds. The N50 value was 23.73 Kb, which suggested that half of the genome assembly was contained in scaffolds greater or equal to this length, and the average length of scaffolds was 2,275 bp. The guanine-cytosine content (GC) and repeat content of the genome were 44.1 and 49.1%, respectively. In total, 57,180 protein-coding genes were identified from this genome, which were classified into 3,254 gene families based on the similarities in Pfam, a database of protein families and domains, of which zinc knuckle, aspartyl protease, leucine-rich repeat, and arabidopsis retrotransposon Orf1 (ATHILA ORF-1) families were found to be expanded. A total of 114,083 simple sequence repeats (SSRs) were identified, of which dinucleotide repeats were dominant (66,805, 58.56%), followed by tri (40,578, 35.57%), tetra (2,179, 1.91%), penta (3,010,

2.64%), and hexa (1,511, 1.32%), respectively. Moreover, the authors identified 11,125 genes containing transcription factor domains, 2,866 genes related to drought tolerance, 1,766 genes related to disease resistance, 330 calcium transport and accumulation-related genes, and 146 C4 pathway genes. The genotype PR202 was sequenced using a combination of Illumina, PacBio, and optical mapping technology, which resulted in the generation of an assembly of size 1,188 Mb, which represented 78.2% of the estimated genome size of PR202.⁸⁶ Compared to the genome assembly of ML-365, the genome assembly of PR202 showed improvements with fewer scaffolds (1,897) and a higher N50 value (2.6 Mb). This indicates that combining long-read technology with short-read technology can significantly enhance the quality of genome assembly.

Foxtail millet

Foxtail millet (*Setaria italica*) is diploid in nature, and the estimated genome size is 485 Mb.⁸⁷ The genome of foxtail millet was sequenced from four cultivars using a combination of different sequencing technologies.⁸⁷⁻⁸⁹ The cultivar 'Zhang gu' was sequenced with Illumina sequencing technology, generating 63.5 Gb of raw data. An assembly of 423 Mb distributed on 439 scaffolds was constructed, which represented 86% of the estimated genome size (485 Mb).⁸⁷ The transposable elements comprised 46% of the genome, dominated by Long Terminal Repeats (LTR). A comprehensive analysis of the Zhang gu genome yielded a total of 38,801 predicted genes. Among these genes, 78.8% were successfully functionally annotated, providing valuable insights into their potential biological roles. Furthermore, based on transcriptome data obtained from various tissues, it was determined that 81.7% of the predicted genes were discovered to be expressed, indicating their active involvement in cellular processes. The authors also utilized the genome information to map an herbicide resistance gene encoding acetyl-CoA, suggesting that this genome data is a valuable resource in future research on foxtail millet. The foxtail millet inbred line 'Yugul' was sequenced using the Sanger method, which yielded an assembly of 396.7 Mb in total.⁸⁷ Later in 2016, the cultivar "TT8" was sequenced on Illumina and Roche 454 platforms and assembled into a total genome of 477 Mb.⁸⁸ Recently, the cultivar "Huagu11" was sequenced using a combination of PacBio and Hi-C mapping technologies, which significantly improved the quality of genome assembly (408.37 Mb) compared to the genome of other cultivars.⁸⁹

Table 3. Assembly statics of millets reference genome.

Si. No	Millet type	Reference genome size (Mb)	Methods for sequencing	Assembly level	Scaffold N50 (Mb)	No. of Scaffold	GC content	Repeat content	No. of predicted genes	Reference genome id (GenBank)
1	Proso millet (<i>Panicum miliaceum</i>)	842	PacBio	Chromosome	48.2	441	46.5	58.2%	55930	GCA_002895445.3
2	Pearl millet (<i>Pennisetum glaucum</i>)	1800	Illumina, Oxford nanopore	Chromosome	259.2	7	49.5	77%	38579	GCA_947561735.1
3	Finger millet (<i>Eleusine coracana</i>)	1200	Illumina MiSeq, NextSeq, PacBio RSII, Bionano Saphyr	Scaffold	23.9	1196	43.5	50%	57180	GCA_021604985.1
4	Foxtail millet (<i>Setaria italica</i>)	405	ABI	Chromosome	47.3	336	46	46	34584	GCF_000263155.2
5	Barnyard millet (<i>Echinochloa crus-galli</i>)	1500	Illumina, PacBio	Scaffold	1.8	4534	45.5	40.7	108771	GCA_900205405.1
6	Sorghum (<i>Sorghum bicolor</i>)	708	Sanger, Illumina	Chromosome	68.7	867	43.5	61	34,118	GCF_000003195.3

Recently, Li *et al.* developed a database called "MDSi" containing resequencing data from 398 germplasms, including 360 foxtail millet and 38 green foxtails, as well as metabolic information.⁹⁰

Proso millet

Proso millet (*Panicum miliaceum*) is allotetraploid ($2n=4x=36$) in nature. The genome was sequenced using the Illumina short-read and PacBio long-read sequencing platforms.⁹¹ The total length of the genome assembly was 855 Mb, which represented 92.3% of the estimated genome of proso millet (955 Mb); 96.1% of the genome assembly (822 Mb) was distributed on 18 pseudomolecules and the rest was assigned to 1291 unassigned contigs. The genome of broomcorn millet has 58.2% repeats. This genome had 112,158 SSRs, with a mean occurrence frequency of 22.5 per Mb. In total, 55,930 protein-coding genes were identified, of which 99.3% (55,527) were found on 18 pseudo molecules and were assigned to 20,374 families based on their functional domain in them. In total, 972,863 SNPs were discovered through the resequencing of 85 unique proso millet accessions from 23 different nations, providing a useful resource for proso millet genome-wide association studies (GWAS).⁹² Recently, the genotyping by sequencing (GBS) analysis of mutant lines for contrasting yields (high yield and low yield) and wild-type proso millet identified 30,335, 31,488, and 25,901 SNPs, respectively. These SNPs can be further used in identifying genes responsible for various metabolic processes in proso millet and in designing useful genetic markers.⁹³

Barnyard millet

Barnyard millet (*Echinochloa crus-galli*) is a naturally occurring allohexaploid with a chromosome number of $2n=6x=54$. The plant exhibits rapid germination and growth, resembling that of rice, while also displaying broad ecological adaptability and a substantial capacity for seed generation (94). The cultivar STB08 was selected for sequencing using Illumina and PacBio technologies (95). A combined sum of 207.4 Gb and 32.9 Gb of genomic data were produced through the utilization of Illumina and PacBio sequencing technologies, respectively. The draft genome of Barnyard millet is 1.27 GB in length with a scaffold N50 length of 1.8 Mb. In total, 108,771 protein-coding genes were predicted from this genome, of which 85% were functionally annotated. The sequence analysis also revealed that the genome of barnyard millet has evolved a large repertoire of detoxification-related genes, and most of them were found to be associated with allelopathic interactions with rice, providing insight into tolerance mechanisms related to biotic and abiotic stresses. This could be a valuable resource to understand the genes involved in climate resilience and their beneficial effects on crop improvement programs.

Sorghum

Sorghum (*Sorghum bicolor*) is the world's 5th most prominent cereal crop. Due to its diploid nature ($2n = 20$) and relatively small and non-duplicated genome, it is considered a genetic model for C4 grasses, and the genomes of several cultivars were sequenced and made available publicly. The first reference genome of sorghum (cultivar BTx623) was sequenced and assembled by Paterson *et al.* in 2009.⁹⁶ Later, this assembly was updated by McCormick *et al.*⁹⁷ The BTx623 genome assembly is 655.2 Mb in length, which represents 89.7% of the estimated genome size of 730 Mb, suggesting that the BTx623 reference genome still needs to be improved using advanced long-reading technology such as PacBio or Oxford

Nanopore sequencing technologies. However, a chromosome-scale assembly of the sorghum genotype Tx430 was made available using Nanopore sequencing and optical mapping technologies, which represented 91.7% of the estimated genome.⁹⁸ Similarly, the genotype 'Rio' was sequenced using PacBio sequencing technology with coverage of 75x of the genome, which generated an assembly of length 729.4 Mb.⁹⁹ The number of genes in the reference genome of sorghum (BTx623) was 34,129 whereas in Tx430 and Rio were 39,510 and 35,476, respectively, suggesting the presence of unique genes in these genotypes. Numerous studies have demonstrated that comprehensive characterization of species gene content variety and improved understanding of species diversity, domestication, and breeding history may be obtained by examining the pan-genome of a large number of genotypes.¹⁰⁰ Recently, Ruperao *et al.* constructed a sorghum pan-genome of size 883.3 Mb using BTx623 reference genomes as well as reads from 354 genetically diverse sorghum accessions belonging to different races.¹⁰¹ The pan-genome exhibited a 24.6% (174.5 Mb) increase in comparison to the reference genome (BTx623). The pan-genome yielded 35,719 predicted genes, of which 53% exhibit presence-absence variation across sorghum accessions. Over two million SNPs were identified from the pan-genome analysis, of which 398 SNPs were found associated with important agronomic traits, of which 92 were in genes.¹⁰¹ Similarly, Tao *et al.* sequenced 13 sorghum accessions representing cultivated sorghum and its wild relatives and integrated them with 3 other published genomes (BTx623, Tx43013, and Rio) to generate a pan-genome of size 954.8 Mb, 30% larger than the 732.2 Mb reference genome.¹⁰² The authors found that the pan-genome shows substantial variances in gene content, with 64% of gene families displaying presence/absence variations among the genome studied. The discovered variants were found to undergo selection during the process of sorghum domestication and improvement, indicating the potential utility of these genes for enhancing crops.¹⁰²

Conclusions and future research directions

Milletts have garnered heightened interest as a promising agricultural crop due to their diverse nutritional and medicinal attributes. Based on the research cited in this review, it is essential to consider millets as part of a balanced and varied diet, combined with regular physical activity and proper medical management for many diseases such as diabetes, cardiovascular diseases, and others. Nonetheless, there exist other domains in which forthcoming research can provide significant additions to our comprehension of millets and their prospective uses. For example, the implementation of meticulously planned clinical trials using human subjects can be employed to examine the precise physiological advantages of millets, particularly in relation to their effects on the management of diabetes, cardiovascular well-being, and digestive issues. These trials have the potential to yield more substantial evidence in support of the medicinal effects of millets. Another fascinating area of study involves doing a thorough investigation to identify the bioactive compounds responsible for the anticancer properties of millets by using a sequence of *in vitro* testing, animal models, and eventually human trials. Another significant field for future research is to understand the impact of millets on the composition and activity of gut microbiota, with a specific focus on their prebiotic qualities. The investigation of the relationship between millets and gut flora can yield valuable knowledge regarding their possible effects on digestive health and general welfare. Another promising area of research involves the investigation of the resilience exhibited by several millet types in response to dynamic climate

circumstances, encompassing factors such as drought, heat stress, and water availability. The identification of millet varieties that exhibit climate resilience has the potential to contribute to the promotion of sustainable agriculture and enhance food security in places that are particularly susceptible to climate-related challenges. Despite the evident nutritional benefits of millets, the underlying mechanism responsible for the synthesis of phytochemicals in these grains has not been well investigated. This suggests the existence of a potential area of study that warrants further investigation. In conclusion, millets, commonly known as the “overlooked cereal,” possess a lengthy historical lineage that extends over numerous millennia and encompasses a wide array of cultures and geographical areas. Despite its enduring existence, it continues to be largely unfamiliar to a significant portion of individuals in the contemporary society. Nevertheless, with the increasing worldwide demand for sustainable and nutritious food sources, millets are emerging as a prominent contender in shaping the future of the food industry.

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