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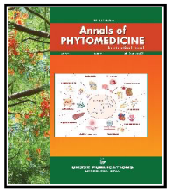

Review Article : Open Access

Exploring the potential of bioactive compounds existing in millets: Implications for health benefits

K. Sibi*, P. Vasuki, G. Vigneswaran***, A. Nandhakumar, A. S. Vishal Pranav, A. Raghav and T. Prabha**◆

Department of Pharmaceutical Chemistry, Nandha College of Pharmacy, Affiliated to The Tamil Nadu Dr. MGR Medical University, Chennai, Erode-638052, Tamil Nadu, India

** Department of Pharmacology, Nandha Dental College and Hospital, Affiliated to The Tamil Nadu Dr. MGR Medical University, Chennai, Erode-638052, Tamil Nadu, India*

*** Department of Pharmaceutical Analysis, Karpagam College of Pharmacy, Othakkalmandapam, Coimbatore-641032, Tamil Nadu, India*

**** Department of Biochemistry, Nandha Dental College and Hospital, Affiliated to The Tamil Nadu Dr. MGR Medical University, Chennai, Erode-638052, Tamil Nadu, India*

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Abstract

Millets, an ancient group of small seeded cereal grains, are increasingly recognized for their potential as sources of phytopharmaceutical bioactive compounds derived from plants that offer significant therapeutic benefits. This review delves into the diverse phytochemicals in millets, including polyphenols, flavonoids, phenolic acids, saponins, tannins, terpenes, alkaloids, sterols, and glycosides, each contributing to the unique health promoting profile of these grains. Known for their antioxidant, anti-inflammatory, and anticarcinogenic properties, millet derived phytopharmaceuticals address a range of chronic health concerns, such as diabetes, cardiovascular disorders, and cancer. For example, polyphenols found in millet grains act as powerful antioxidants, reducing oxidative stress, while saponins and sterols help manage cholesterol levels, supporting cardiovascular health. With the global demand for natural and functional foods on the rise, millets stand out as sustainable, plant based solutions to lifestyle diseases. This aligns with regulatory shifts, particularly in India, where phytopharmaceuticals are being increasingly recognized on par with synthetic drugs, encouraging further research and investment in millet based therapeutics. By incorporating millets into everyday diets, consumers may access a natural, cost effective approach to disease prevention and management, contributing to both personal and public health. This review underscores the potential of millet derived phytopharmaceuticals to play a crucial role in preventive healthcare, paving the way for their inclusion in future functional foods and nutraceutical innovations.

1. Introduction

Phytopharmaceuticals, derived from plants, are bioactive compounds that possess medicinal properties and offer significant therapeutic benefits. They have gained increasing attention due to their ability to act as natural remedies for a wide range of diseases, with minimal side effects compared to conventional pharmaceuticals. The growing interest in phytopharmaceuticals can be attributed to their multifunctional roles, including antioxidant, anti-inflammatory, anticarcinogenic, antimicrobial, and antidiabetic activities (Karthikeyan *et al*., 2024; Sivakumar *et al*., 2022). Such properties make them promising candidates for the development of natural therapies aimed at addressing both chronic and acute health issues.

Millets, a group of small seeded grasses, have been cultivated for thousands of years and are widely consumed in many regions, particularly in Africa and Asia (India). Indian farmer grows several species (Figure 1) such as pearl millet (*Pennisetum glaucum*), finger millet (*Eleusine coracana*), foxtail millet (*Setaria italica*), and sorghum (*Sorghum bicolor*) (Saleh *et al*., 2013). These ancient grains have recently gained attention not only for their resilience in harsh environmental conditions, but also for their significant phytochemical value in public health. These small seeded grains are rich in a variety of phytochemicals such as phenolic acids, flavonoids, tannins, phytosterols, and saponins. These compounds contribute to the health-promoting properties of millets. These bioactive compounds exhibit antioxidant, anti-inflammatory, antidiabetic, and cardioprotective properties, making millets a potential dietary intervention for lifestyle related diseases (Duraisami *et al*., 2021; Saleh *et al*., 2013). For example, phenolic acids present in finger millet have been shown to exhibit potent antioxidant activity, helping to reduce oxidative stress and mitigate the risk of inflammation driven diseases (Devi *et al*., 2014). Similarly, the phytosterols found in millets may aid in lowering cholesterol levels, which is critical for heart health (Srivastava and Sharma, 2019). As consumers and researchers alike focus on the role of diet in promoting health and preventing chronic diseases, millets have emerged as an important food crop due to their rich composition of bioactive compounds and essential nutrients (Chandrasekara and Shahidi, 2011).

Corresponding author: Dr. T. Prabha
Professor and Head, Department of Pharmaceutical Chemistry, Nandha College of Pharmacy, Erode-638052, Tamil Nadu, India
E-mail: drtpappa@yahoo.com
Tel.: +91-9965557346

Approximately 65-75% of millets are made up of carbs, 7-12% proteins, 2-5% fat, and 8-15% fibre. Compared to traditional cereals, they contain more necessary amino acids, and millets' prolamin improves the digestion of proteins. There is strong scientific evidence that eating millets lowers the risk of atherosclerotic cardiovascular disease, improves glycemic index (GI), lowers body mass index, and slows the course of prediabetes. Millets' high levels of resistant starch and slowly digested starch reduce postprandial insulin and glucose excursions. Millets are the preferred diet for those with coeliac disease since they are gluten-free. Millets are becoming more popular as weaning and health-conscious foods because of their high nutritional content. By promoting satiety, phytochemicals like proanthocyanidins, which are found in millets' grain and bran, have antiobesity properties (Jacob *et al*., 2024).

Millets are an excellent source of nourishment. Millets are becoming increasingly popular both in India and around the world because of their potential to provide food security, environmental sustainability, and nutritional value. As part of wider measures to address global issues including malnutrition, climate change, and sustainable agriculture, both Indian and international programs are attempting to increase the production, consumption, and knowledge of millets. In order to promote the production and consumption of millets and to increase awareness of their significance as a food crop, the Food and Agricultural Organisation of the United Nations (FAOUN) launched the IYOM 2023 worldwide campaign. Millet awareness and consumption have increased in recent years as individuals have begun to pursue a healthier lifestyle. In 2018, India suggested 2023 as the International Year of Millets. The FAOUN accepted it, and the UN general assembly declared 2023 to be the 'International Year of Millets'.

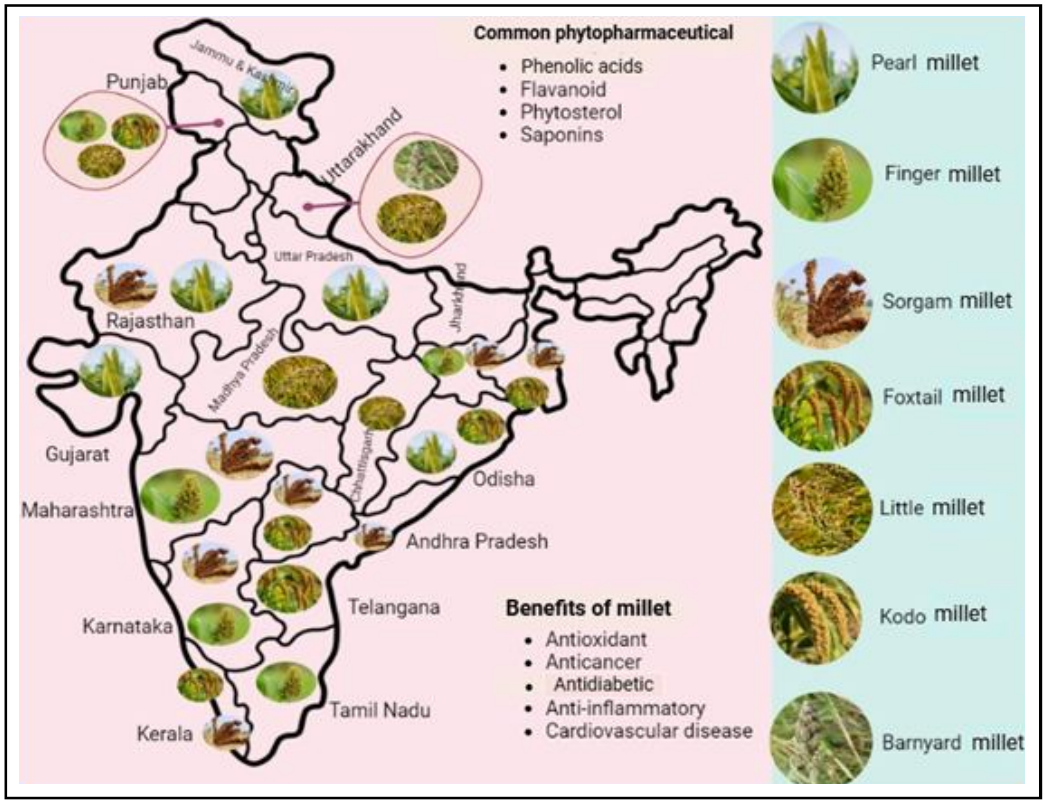


Figure 1: Geographical distribution of different species of millets in India.

The rising demand for natural, sustainable, and holistic healthcare options has further fuelled research into the potential of phytopharmaceuticals. As more scientific evidence accumulates, the role of phytopharmaceuticals is expected to expand, making them integral to the future of preventive healthcare, functional foods, and nutraceuticals (Patwardhan and Mashelkar, 2009). By integrating millet derived phytopharmaceuticals into daily diets, individuals may benefit from accessible, cost effective ways to manage and prevent various health conditions. Their natural origin also aligns with the increasing consumer preference for plant-based products over synthetic alternatives.

The aim of this review is to explore the phytopharmaceutical potential of millets by focusing on their bioactive compounds and health benefits. Given the increasing prevalence of lifestyle diseases such as diabetes and cardiovascular disorders, understanding how millet derived phytopharmaceuticals can mitigate these conditions is of growing importance (Zhu, 2021). This comprehensive review provides insight into the various phytochemicals found in millets, their therapeutic benefits, and the potential role of millets in the development of novel functional foods and nutraceuticals. In this context, the public's reliance on traditional medicine is not just a reflection of cultural practices but also a response to global health challenges, including the rising cost of pharmaceutical drugs and the emergence of drug-resistant diseases (Ekor, 2014). Traditional plant based remedies offer a natural, often safer, alternative or complement to synthetic drugs, and their importance is likely to grow as more people seek out natural, accessible, and holistic healthcare options (Chethan and Malleshi, 2007).

2. Salient features of phytopharmaceuticals

The drug controller general of India aims to provide natural derived drugs with the same regulatory status as synthetic, compound based drugs. This approach would foster in-depth biomedical evaluation of these novel treatments, supporting the broader integration and acceptance of herbal products in modern medical practice (Meyer and Staden, 2000). Globally, there is growing interest in natural compounds as promising therapeutic sources for unmet medical needs, bringing this goal closer to reality. Once the new regulation is finalized, national laboratories, scientific groups, and industrial R and D units focused on botanical leads will have a streamlined path to obtain marketing authorization. This shift will likely encourage innovation and attract investors toward developing plant-based therapies (Bohm and Kocsy, 2016; Newman and Cragg, 2016; Ishika Choudhary, 2021). Unlike psychoactive drugs, which typically focus on single targets, herbal medicines contain a rich array of natural compounds that act on various biological systems. Evidence based phytopharmaceuticals, increasingly referenced in clinical practice guidelines, and is now recognized as frontline therapies for multiple diseases and health indications. Numerous classical medications, including morphine for pain relief and atropine, originated from plant-based compounds. Today, the demand for clinically validated phytopharmaceuticals is high, with their safety and efficacy confirmed through rigorous randomized, controlled clinical trials (Jha and Gupta, 2021; Ishika Choudhary, 2021).

3. Phytopharmaceuticals in millets

Table 1: Phytopharmaceuticals in Indian grown millets

Millet name	Phytopharmaceuticals	Processing method	Nutritional aspect	Reference
Sorghum bicolor L. (GI = 62-70)	Salicylic, protocatechuic, caffeic, sinapic, ferulic acids, p-coumaric acid, phenolic acids (gentisic, cinnamic); flavonoes (luteolin, tricin, and apigenin); flavonones (eriodictyol and naringenin);	Fermentation	Antioxidant capacity	Mohammed *et al*., 2022; Mawouma *et al*., 2022
		Malting	Fat, carbohydrate, protein, calcium and iron	Mawouma *et al*., 2022; Davana *et al*., 2021
		Germination	Essential amino acids	Mawouma *et al*., 2022; Saithalavi *et al*., 2021
Eleusine coracana L. (GI = 54-68)	Phenolic acids (gallic, vanillic, querticin, caffeic, FA, p-CA): flavonoids (catechin equivalent)	Fermentation	Protein content, phenolic content copper, iron, manganese, zinc	Anis and Sreerama, 2020; Jan *et al*., 2022; Narayanasam, 2021
		Germination	Iron, zinc, calcium, essential amino acids	Anis and Sreerama, 2020; Kazi *et al*., 2022
		Malting	Vitamin C	Anis and Sreerama, 2020; Kazi *et al*., 2022
Pennisetum glaucum L. (GI = 55)	3- deoxynthocyanidin; phenolic acids (gallic, vanillic, chlorogenic acid, sinapic acid, ferulic acids, p- coumaric acid)	Fermentation	Phenol, soluble protein, amylase glucose, calcium, zinc, iron	Pujari and Hoskeri, 2022; Eghune *et al*., 2022
		Germination	Lysine, methionine	Pujari and Hoskeri, 2022; Budhwar *et al*., 2020
		Malting	Protein and starch digestibility	Pujari and Hoskeri, 2022; Bajaj *et al*., 2022
Setaria italica L. (GI = 50-60)	Phenols (apigenin, N'-caffeoyl-n'- feruloylspermidine, di-p-coumaroyl spermidine, n,n',n''- diferuloyl spermidine- dihexoside); carotenoids (xanthophyll, zeaxanthin)	Fermentation	Protein, copper, iron, manganese	Anis and Sreerama, 2020; Jan *et al*., 2022; Kumari *et al*., 2023
		Germination	Phenolic acids, flavonoids	Anis and Sreerama, 2020; Jan *et al*., 2022; Kumari *et al*., 2023; Santra *et al*., 2019
Paspalum scorbiculatum L. (GI = 52.7)	Phenolic acids (stigmasterol, campesterol, N-(5- hydroxypentyl) arachidonoylamide, pregnenolone)	Fermentation	Protein, amino acids availability and starch digestibility	Sharma *et al*., 2021; Boukail *et al*., 2021; Bunkar *et al*., 2021

		Malting	Antioxidants, proteins, fats, carbohydrates	Sharma *et al*., 2021; Boukail *et al*., 2021; Bunkar *et al*., 2021
Panicum sumatrense Roth. (GI = 52.11)	Flavonoids (6-C- glucosyl-8 -C- arabinosyl apigenin); phenol (sinapic acid, p-coum-arylpentose, synapaldehyde, kaempferol)	Fermentation	Copper, iron, protein content, manganese, zinc, phenolic content	Sarita and Singh, 2016; Taylor, 2019
		Malting	Starch digestibility and protein	Sarita and Singh, 2016; Taylor, 2019
		Germination	Flavonoids, and phenolic acids	Sarita and Singh, 2016; Taylor, 2019

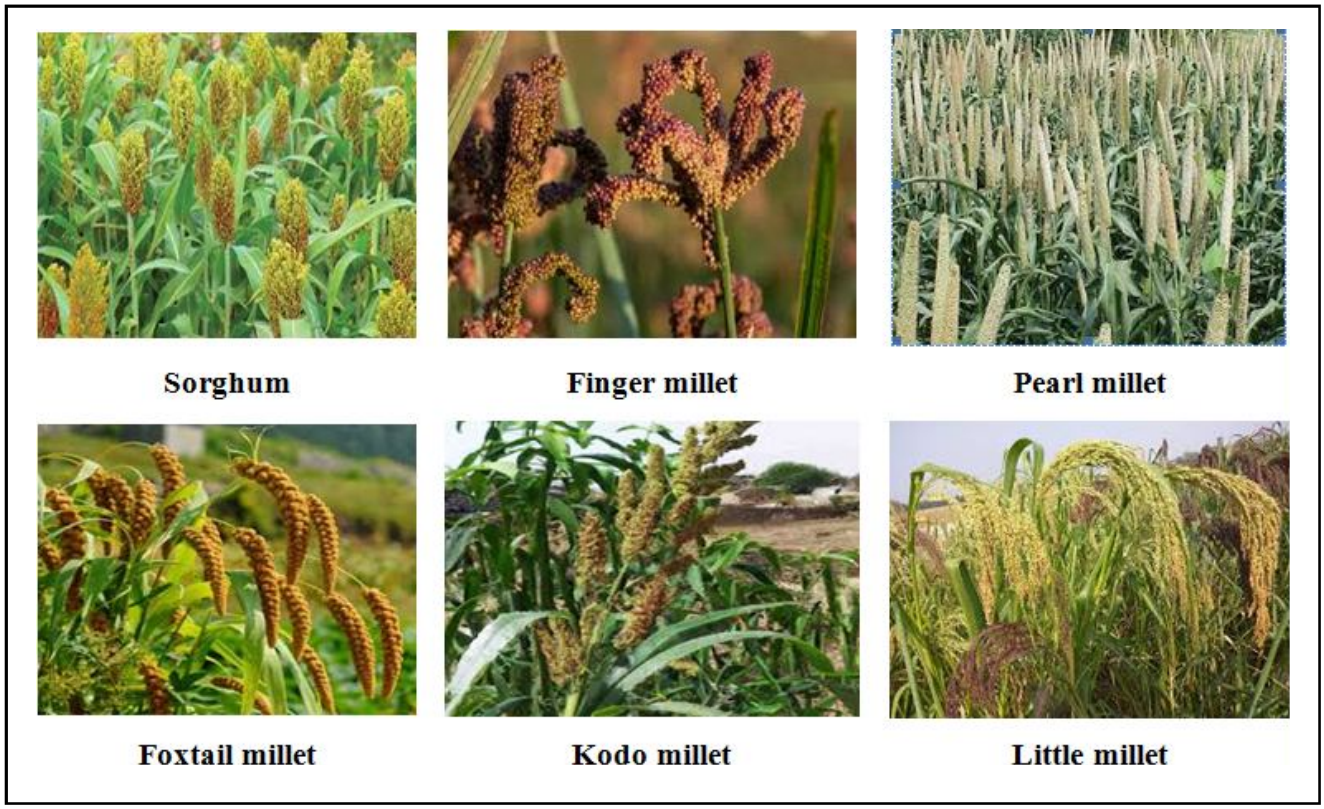


Figure 2: Assorted millets verities available in India.

3.1 Polyphenols

Polyphenols are intermediates in metabolic pathways that function as defense and signaling molecules, contributing to essential biological processes (Sri Bhuvaneswari *et al*., 2023). In millets, phenolic acids and flavonoids are the primary polyphenol groups (Duodu and Awika, 2019). These compounds contribute to the significant antioxidant properties of millets in both dietary and biological contexts (Kharat *et al*., 2019). The seed coat of millets is especially rich in dietary fiber and polyphenols. Phenolic compounds are known for their pH sensitivity and are highly heat stable under typical conditions (Tripathi *et al*., 2021). Research suggests that millet consumption may reduce free radical induced stress in the hippocampus and downregulate genes such as γ-secretase, tau, and amyloid precursor protein, which are associated with alzheimer's disease (Li *et al*., 2020). Millet derived polyphenols also show antidiabetic properties, displaying specific hypoglycemic effects (Wang *et al*., 2022). Furthermore, bound polyphenols from millet bran, including p-coumaric acid (p-CA) and ferulic acid, demonstrate anticancer activity. These compounds enhance the sensitivity of drug resistant colorectal cancer cell lines to oxaliplatin, a chemotherapy drug for colorectal cancer cell lines (Zhang *et al*., 2021). Additionally, foxtail millet polyphenols induce apoptosis, inhibiting colorectal cancer progression in mice. Millet bound polyphenols also exhibit immunomodulatory and antifungal properties (Shi *et al*., 2015).

3.2 Phenolic acids

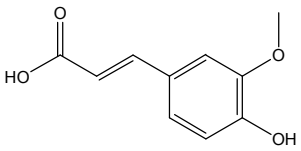
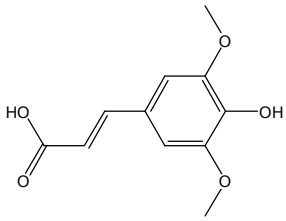
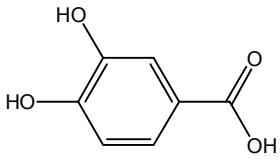
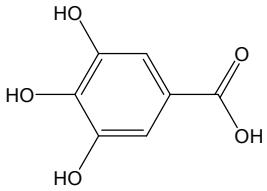
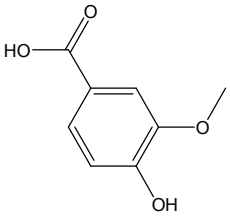
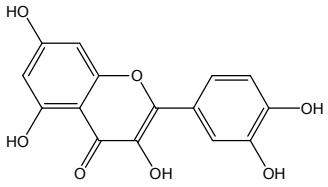
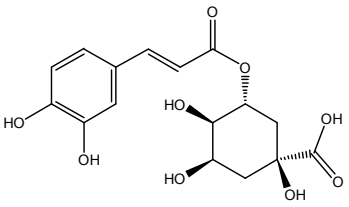
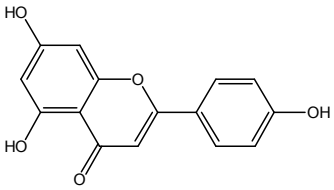
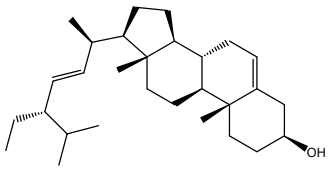
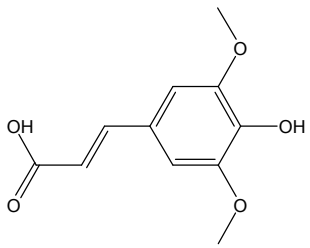
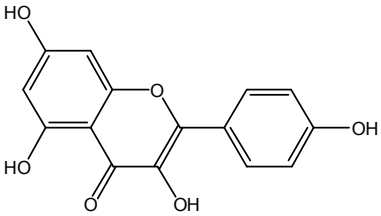
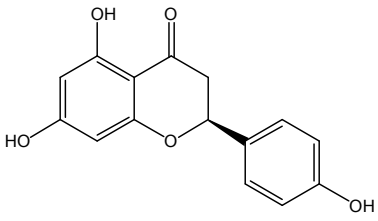
Millets, phytochemicals, and their phenolic acids in millets originate from hydroxybenzoic acid and hydroxycinnamic acid, with content varying by millet species. Phenolic acids are found in both non-conjugated and free soluble forms (Shahidi *et al*., 2013). The primary bound phenolic acids are derivatives of cinnamic acid, such as coumaric

and caffeic acids, while free, unbound forms are typically derivatives of gallic acid, including syringic and vanillic acids (Duodu and Awika, 2019). Notably, bound phenolic acids possess significant antioxidant and therapeutic properties, which are beneficial in promoting gut microbiota health and supporting overall gut function (Selma *et al*., 2009).

3.3 Flavonoids

Millets are rich in various flavonoid compounds, including flavones, flavanols, flavanones, anthocyanins, chalcones, and amino phenols (Chandrasekara and Shahidi, 2011). Flavonoids are the primary class of polyphenols in millets, contributing valuable preservation qualities that support a balanced diet. Millet flavonoids are potent antioxidants, surpassing elements like zinc, selenium, and certain vitamins in antioxidant strength (Sokol-Letowska *et al*., 2006). Sarita and Singh, (2016) reported that millet flavonoids exhibit numerous health benefits, including anticancer, diuretic, antihypertensive, analgesic, hypolipidemic, and anti-inflammatory effects. Their antihypertensive and antiarrhythmic effects include the relaxation of smooth muscle in the heart, alongside LDL cholesterol oxidation prevention (Duarte-Alameida *et al*., 2007). Flavonoids also contribute to cholesterol reduction and inhibit platelet aggregation, while modulating the body's response to pathogens and helping to control allergens (Middleton *et al*., 2000).

Table 2: Chemical structures of some of the phytoconstituents present in millets

 Ferulic acid	 Sinapic acid	 Protocatechuic acid
 Gallic acid	 Vanillic acid	 Quercetin
 Chlorogenic acid	 Apigenin	 Stigmasterol
 Sinapic acid	 Kaempferol	 Naringenin

3.4 Alkaloids

Alkaloids play a crucial role in enhancing a plant's fitness and exhibit pharmacological effects, often utilized in medications and as recreational drugs. As nitrogen containing compounds, they provide several health benefits. However, alkaloids can also have genotoxic, mutagenic, carcinogenic, fetotoxic, and teratogenic effects (Weidenfield, 2011). In foxtail millet, alkaloids have demonstrated antihyperglycemic and hypolipidemic effects in diabetic rat models (Bhat *et al*., 2021). Despite their health benefits, the potential harmful effects of alkaloids warrant caution.

3.5 Terpenes

Plant phytosterols are produced through biosynthetic pathways, with isopentenyl pyrophosphate as a key building block for terpenoids (Shah *et al*., 2021). Terpenes, the chemical compounds responsible for the distinct aroma and flavor of millets, are primarily found in essential oils and enhance the nutraceutical qualities of the plant. These include linalool, geraniol, myrcene, and limonene (David *et al*., 2014). Terpenes contribute to both the sensory characteristics and health benefits of millets. Traditionally, terpenes have been valued for their roles in medicinal systems, with further potential as antineoplastic and antibacterial agents.

3.6 Saponins

Saponins are known for their ability to create a soapy lather when mixed with water and have been linked to reductions in blood cholesterol levels upon ingestion. In millets, this phytochemical is primarily found in the seed coat or outer grain layers (Bhuvaneshwari *et al*., 2020). Finger and pearl millets are particularly rich in saponins, with pearl millet having the highest content. Compared to cereals and grasses, millets generally contain more saponins (Sharma *et al*., 2023). Saponins exhibit valuable physicochemical and biological properties, making them beneficial in the food industry as emulsifying agents that improve bread porosity and aerate culinary items. They also serve as key ingredients in detergents, shampoos, and animal nutrition, and function as natural biocontrol agents due to their wetting abilities (Sharma *et al*., 2023). Medicinally, saponins offer a variety of benefits, including anti-inflammatory, anticancer, antioxidant, and cholesterol lowering effects (Jha and Gupta, 2021).

3.7 Tannins

Millets comprise up to 0.61% of polyphenolic chemical substances called tannins (Sheethal *et al*., 2022). Millets' antioxidant capabilities, which lower aging and improve metabolic processes, are attributed to their tannins (Dey *et al*., 2022). Cultivars of millet with increased tannin content have better antioxidant qualities (Siwela *et al*., 2007). The antioxidant properties of finger millet grains with tannins are higher than those of grains without tannins. Since they have their strong antimineral absorption properties, tannins are regarded as antinutrients. It appears that different millet species have differing contents. Processing millets to increase their bio accessibility and reduce their tannin content can lessen their antinutritional properties.

3.8 Sterols

Millet sterols, present as naturally occurring phytosterols, are secondary metabolites and essential components of plant cell membranes (Sharma *et al*., 2021). Some commonly found sterols in millets include episterol, 24-methyllathosterol, brassicasterol, avenasterol, 24-ethyllathosterol, 24-methylenecholesterol, isofucosterol, fucosterol, 24-methyl-5α-cholest-24-en-3β-ol, and 24-ethyldesmosterol. These sterols are typically found in millet seeds and are known for their cardiovascular benefits due to their structural similarity to cholesterol. By competing with cholesterol for absorption in the intestines, millet sterols effectively reduce cholesterol levels in circulation. As a result, regular millet consumption supports a balanced diet, promoting overall health and wellbeing (Jha and Gupta, 2021). Fortifying millet products by increasing sterol content can enhance their nutritional value (Piironen *et al*., 2002).

3.9 Glycosides

Glycosides in millets are compounds formed by sugar molecules linked to other functional groups. Key glycosides in millets include kaempferol glucoside, catechin, epicatechin glucoside, and glucosyl orientin (Sharma *et al*., 2021). Millets also contain esterified sterol glycosides and sterol glycosides, which are classified as millet glycolipids. These glycosides, as phenolic compounds in millet grains, contribute to reducing the risk of chronic diseases and enhance the antioxidant and anti-inflammatory properties of millets (Devi *et al*., 2014). This phytochemical enriches millets' overall nutritional profile and health benefits (Singh *et al*., 2022). Additionally, millet malts contain higher levels of free sugars and non-starchy water-soluble polysaccharides compared to unprocessed millets.

4. Conclusion

The phytopharmaceutical potential of millets underscores their significance as a valuable resource for promoting health and preventing lifestyle related diseases. The diverse bioactive compounds present in millets, including polyphenols, flavonoids, alkaloids, terpenes, saponins, tannins, sterols, and glycosides, collectively contribute to their antioxidant, anti-inflammatory, antidiabetic, and cardioprotective properties. As consumers increasingly seek natural alternatives to synthetic pharmaceuticals, millets represent a sustainable and accessible solution to addressing chronic health issues. The regulatory support from the Drug Controller General of India for natural derived drugs aligns with the growing global interest in phytopharmaceuticals. This shift paves the way for rigorous scientific evaluation, encouraging innovation and investment in the development of plant based therapies. The recognition of clinically validated phyto-pharmaceuticals as frontline treatments further emphasizes the need to integrate these natural remedies into contemporary healthcare practices. As research continues to reveal the health benefits and therapeutic potentials of millet derived phytopharmaceuticals, there is a promising outlook for their incorporation into functional foods and nutraceuticals. By enhancing public awareness and acceptance of these natural products, we can promote healthier dietary choices and provide effective solutions for managing various health conditions. Ultimately, the revitalization of traditional plant based remedies, coupled with scientific validation, presents a holistic approach to healthcare that resonates with the growing preference for natural, sustainable solutions in modern society.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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