Pharmacogn Rev. 2022;16(32):100-106
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
www.phcogrev.com | www.phcog.net

Review Article

Minor Millet Phytochemicals and their Pharmacological Potentials

Nivedita Pujari S, Joy H Hoskeri*

ABSTRACT

Minor millets (MMs) belong to one of the most ancient groups of cereals consumed in different parts of the world. Minor millets are less known grains because of lower cultivation rates and lesser consumption rates. However, MMs area rich source of nutrients, including vitamins, protein, fiber, and starch. GC-MS, LC-MS, and HPLC are commonly used techniques for the phytochemical profiling of MMs. Methanol extracts of MMs have been reported to possess the majority of potential phytochemicals that include flavonoids, terpenoids, sterols, phenols, xanthophylls, xanthinin's and carotinoids. Some of the most reputed phytochemicals reported include Octadecenoic acid, Stigmasterol, Campesterol, Phthalic acid, Hexadecanoic acid, Ascorbic acid, Luteolin, Tricin. Caffeic acid, r-coumaric acid, xanthophylls, b-cryptoxanthin, Gallic acid, Gentisic acid, Vanillic acid, Kaempferol, Coumaric acid, Sinapic acid, Ferulic acid, Vanillicacid hexoside, p-Hydroxybenzoic acid, Homocitric acid, Caffeic acid, N′, and Apigenin-C-dihexoside. These MMs phytochemicals are also reported to exhibit various health benefits, including antioxidant activity, antidiabetic activity, antihyperlipidemic activity etc. Exploring the potential phytochemicals in all known MMs, namely, barnyard millet, kodo millet, foxtail millet, porso millet, and little millet has revealed new insights in understanding these compounds and their potential therapeutic role against disease management.
Keywords: Minormillets, Phytochemicals, Antihyperlipidemia, Antioxidant, Antiproliferative.

Nivedita Pujari S, Joy H Hoskeri*

Department of Bioinformatics, Karnataka State Akkamahadevi Women's University, Vijayapura, Karnataka, INDIA.

Correspondence

Dr. Joy Hoskeri,

Department of Bioinformatics, Karnataka State Akkamahadevi Women's University, Vijayapura-586108, Karnataka, INDIA.

E-mail: joy.kswuv@gmail.com

History

- Submission Date: 23-03-2022;
- Review completed: 28-04-2022;
- Accepted Date: 09-05-2022.

DOI : 10.5530/phrev.2022.16.15

Article Available online
http://www.phcogrev.com/v16/i32

INTRODUCTION

Minor millets (MMs) are a group of underutilized cereals and are reported to be one of the earliest food grains known.[1] Decreased cultivation rate of minor millets is known to be mainly because of lesser consumption rates and due to the increased post-harvest grain processing time.[2] However, recently a few varieties of minor millets are produced by the agriculture sector leading to improved processing aids with decreased time of consumption. Minor millets include foxtail millet *(Setaria italica)*, kodo millet *(Paspalum sorobiculatum)*, little millet *(Panicum sumatrense)*, barnyard millet *(Echinochloa corona)*, and porso millet *(Panicum miliaceum)* (Figure 1).

The change in lifestyle and unhealthy food habits have led to an increase in the rate of chronic diseases, mainly diabetes, inflammatory diseases, cancer, and obesity, in developed and developing countries. The use of synthetic drugs has become a major approach in the management of these diseases. Complications associated with synthetic drugs[3] have bought a whole new era in the pharmaceutical industry and thus, the search for novel and natural compounds is always in focus. Phytochemicals are natural compounds synthesized in the plant systems that project as potential health benefiting agents.[4] Such compounds can be used as agents to treat or manage diseases. Scientists have explored diverse groups of phytochemicals and their derivatives in MMs that are capable of regulating disease.[5-7] Phytochemicals present in minor millets are mainly found in methanol and ethanol extracts, which further screening through chromatographic techniques like HPLC, LC-MS, and GC-MS identifies specific compounds.[8] Minor millet phytochemicals mainly include phenols, polyphenols, flavonoids, carotenoids, and serotonin derivatives.[6,9-11] Health-promoting ability of minor millet phytochemicals mainly involves antioxidant activity, antidiabetic activity, antimicrobial activity, anti-proliferative activity, and anti-inflammatory activity.[12-14]

SEARCH STRATEGY OF ARTICLES

Databases and search engines used for the study included Google Scholar, Pubmed, Scopus, and Pubchem from which title-related research articles, review articles, and book chapters were searched. The keywords used for analyzing the articles included kodo millet, barnyard millet, foxtail millet, porso millet, little millet, phytochemicals, antioxidant activity, antidiabetic activity, antiproliferative, antimicrobial and anti-inflammatory activity. The articles covered in this review are encompassing a large period of publication years with a limiting year of this publication. Results obtained from the

Cite this article: Pujari N, Hoskeri JH. Minor Millet Phytochemicals and their Pharmacological Potentials. Pharmacog Rev. 2022;16(32):100-6.

Figure 1: Driedgrains of A) Little millet, B) Porso Millet, C) Foxtail Millet, D) Barnyard Millet, E) Kodo Millet.

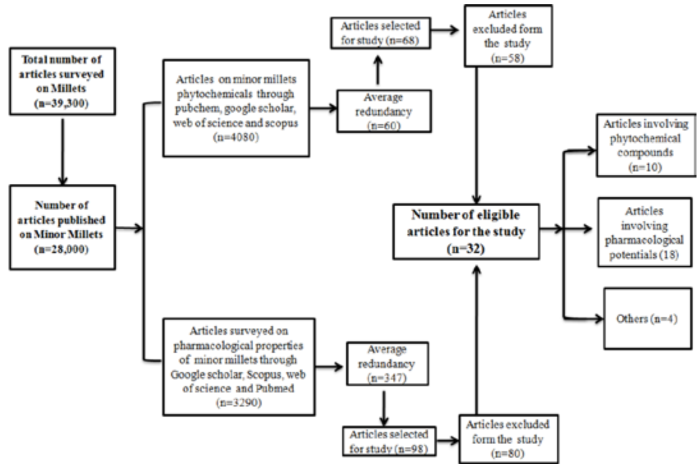

Figure 2: Flowchart of minor millet phytochemical and pharmacological information processing.

search were examined for the presence of various phytochemicals and specific phytocompounds that were analyzed through chromatographic techniques. Both *in-vitro* and *in-vivo* studies investigated with phytochemicals of minor millets were also examined to understand the potential therapeutic properties. Molecular weights and compound names were crosschecked using Pubchem database and listed in different tables. Therapeutic applications of minor millets obtained from both review articles and research articles were considered in the study. Figure 2 describes a consolidated flow chart of the search strategy.

PHYTOCHEMICALS OF MINOR MILLETS

Millets are considered Nutri-cereals and are also known to contribute to potential health benefits, thus MMs have gained much interest from scientists in recent years.[15] Phytochemicals present in millets contribute in enhancing the nutritional value of grains and allow researchers to investigate the potential health benefits of such nutritional grains. According to the classification given by Indian Institute of Minor millets, they are mainly grouped as kodo millet, barnyard millet, porso millet, little millet, and foxtail millet and are reported to be mainly rich in phenols,[16] flavonoids[17] and phytosterols.[18] Even though studies have reported the presence of other phytochemicals such as saponins, tannins, terpenoids, and alkaloids, the exact characterization of these compounds has not yet been investigated. Therefore, the phytochemicals present in minor millets, mainly in barnyard millet and little millet are yet unexplored, thus the current data that is compiled in this review will be showcasing the overall minor millet phytochemicals that contribute in promoting health benefits. Molecular wrights of phytochemicals given in the below tables are from pubchem database.[21]

KodoMillet

Kodo millet (*Paspalum scrobiculatum*) is one among the well-known minor millet crops grown in different regions of the country and is known to be cultivated in India since 3000 years.[1] Kodo millet is known with different vernacular names such as cow grass, ditch grass, and harka in Kannada language. This millet is a potential source of protein and dietary fiber that is also known to be easily digestible.[7] Phytochemical analysis reported on different crude extracts of kodo millet, mainly methanol, ethyl acetate, ethanol, and chloroform extracts have majorly indicated the presence of phenolic acids, tannins and flavonoids. Where the highest total phenolics content and total flavonoid content were reported in ethanol extract with 175.94±1.018 mgGAE/g and 16.48±1.57 mg RE/g extracts respectively.[8] Combined GC-MS analysis of Kodo millet flour has revealed the presence of potential phenol compounds (Table 1) and showed an increase in total phenolics and total flavonoid content during germination.[8] Methanolic extract of kodo millet was reported to show considerable amounts of tannins[19] and phyticacid.[20]

Barnyard millet

Barnyard millets (*Echinochola frumentacea*) are a group of cereals that are mainly consumed in Asian countries, mainly Pakistan, Nepal, and India. Scientific investigators have reported that the barnyard millet is a good source of fibre and protein.[22] However, reports on phytochemical analysis on barnyard millet are limited. Aqueous and methanol extracts of different forms of barnyard millet, *viz.*, soaked, germinated and raw millet indicated the presence of phenolics, alkaloids, saponins, flavonoids, terpenoids and Methanol extracts with highest phenolic content have shown antioxidant activity.[13] Watanabe1999 isolated phytochemicals from ethanol extracts of the Japanese variety of barnyard millet (Table 2) consisting mainly of serotonin and flavonoid compounds. All of these

Table 1: Phenolic compounds isolated from kodomillet.[8]

Sl. No	Phytochemicals	Molecular weight(g/mol)
1.	N-(5-Hydroxy-pentyl)arachidonoylamide	389.6
2.	Pterin-6-carboxylicAcid	207.15
3.	N(3,5-Dinitropyridin2yl)L-asparticacidester	300.18
4.	N-Propyl9,12,15-octadecatrienoate	320.5
5.	Pregan20one,2,hydroxyl-5,6epoxy,15-methyl	346.5
6.	Hexadecanoicacid	256.42
7.	9, Octadecenoicacid	282.5
8.	Butyl6,9,12,15, octadecatetraenoate	332.5
9.	Stigmasterol	412.7
10.	Pregnenolone	316.5
11.	Campesterol	400.7

Molecular weight given in the table is an extract from the Pubchem database.[21]

Table 2: Compounds identified from Japanese barnyard millet.[9]

Sl. No	Name of the compound	Phytochemical group	Molecular weight (g/mol)
1	*N*-(*p*-coumaroyl)serotonin	Serotonin	322.4
2	Luteolin	Flavonoid	286.2
3	Tricin	Flavonoid	330.29

Molecular weights given in the table are from the Pubchem database[21]

compounds were extracted by Sephadex LH-20 chromatography and preparative high-performance liquid chromatography and all compounds were shown to be exhibiting antioxidant activity.[9]

Barnyard millet phytochemical content fluctuates and is influenced by germination time. Therefore, optimized germination of barnyard millet has shown the highest antioxidant activity. Quantitative analysis of phenolic compounds isolated from raw and germinated barnyard millet has shown considerable variation in the concentration of compounds. Phenolic compounds from barnyard millet are listed in Table 3.[23] Antioxidant activities of barnyard millet phytochemicals are reported to show good quantities of phenols, flavonoids, and tannins.[24]

Porso millet

Porso millet (*Panicum miliaceum* L.) is one of the prominent minor millets grown in tropical regions of various countries and it is also believed to be the staple food of low-income populations in some countries. Porso millet grains have rich nutritional properties consisting of proteins, vitamins, and minerals. The grains are also gluten-free and easily digestible. Phytochemical analysis of porso millet grains has indicated the presence of rich sources of phenols, flavonoids and phytates.[11] Gumi 20, Mizao 52, Mi2504-6 are three different Chinese porso millet varieties whose phytochemical analysis is reported as to show the presence of phenolics and flavonoid compounds in aqueous extract. Investigators have reported phytochemical compounds isolated from the Chinese variety porso millets through RP-HPLC[14] and are listed in Table 4. HPLC-Mass spectroscopy analysis of phenolic extracts of porso millet samples from Srilanka has also shown rich sources of frolic acid and P-comuric acid specially found in bound phenolic fractions.[5]

Table 3: Phenolic compounds identified from barnyard millet[23]

Sl. No	Name of the compound	Molecular weight (g/mol)
1.	Phthalicacid, hept-4-ylisobutylester	166.13
2.	Hexadecanoicacid	256.42
3.	Campesterol	400.7
4.	Lupeol	426.7
5.	9,12-Octadecadienoicacid	280.4
6.	Ascorbicacid2,6-dihexadecanoate	176.12
7.	Sitosterol	414.7
8.	Phthalicacid	166.14

Molecular weights given in the table are from the PubChem database.[21]

Table 4: Phytochemical compounds isolated from Gumi 20, Mizao 52, Mi2504-6[5]

Sl. No	Name of the compound	Phytochemical	Molecular weight(g/mol)
1	Chlorogenic acid	Phenols	354.31
2	Syringic acid	Phenols	198.17
3	Caffeic acid	Phenols	180.16
4	r-coumaric acid	Phenols	164.16
5	Ferulic acid	Phenols	194.18
6	xanthophyll,	Carotenoids	568.9
7	zeaxanthin,	Carotenoids	568.8
8	b-cryptoxanthin	Carotenoids	552.85

Molecular weights given in the table are from Pubchem database[21]

Moreover, nine porso millet varieties from China including five waxy and four non-waxy types consist of the highest amount of phenolics, flavonoids, and saponins. Therefore, due to the presence of good amount of phytochemicals, porso millet grains are widely known for health-promoting attributes.[25]

Little millet

Little millet (*Panicum sumatrense*) is another group of important cereals that belong to minor millet. Little millet is grown in several parts of the world and is known to be originated from Southeast Asia. Phytochemicals present in little millet are not yet completely explored; however, a few studies have reported the presence of phenols and flavonoids.[5] Fractions of phenolic compounds present in methanol extracts of little millet are reported to contain potential phytochemicals[6] (Table 5).

Foxtail millet

Foxtail millet (*Setaria italica*) is also one of the oldest known minor millet crops in Africa, which further spread to different countries.[26] This millet is rich in nutraceutical properties containing protein, starch, vitamins, fatty acids and minerals.[27] Foxtail millet is one among the important crops grown and exported in Northern China.[28] Phytochemistry of foxtail millet has been widely explored for understanding its potential benefits. HPLC analysis of methanol extract of foxtail millets has revealed the presence of potential phytochemicals, mainly phenolics, carotenoids, and flavonoids. Foxtail millet phytochemicals reported by various investigators are listed in Table 6.

Table 5: List of phenols and flavonoids present in little millet.

Sl. No	Name of the compound	Phytochemical	Molecular weight (g/mol)	Reference
1	Gallicacid	Phenol	170.12	[6]
2	Proto-catechuicacid	Phenol	154.12	[6]
3	p-Hydroxybenzoicacid	Phenol	138.12	[6]
4	Gentisicacid	Phenol	154.12	[6]
5	Vanillicacid	Phenol	168.14	[6]
6	Syringicacid	Phenol	198.17	[6]
7	Kaempferol	Phenol	286.23	[6]
8	trans-Cinnamicacid	Phenol	148.15	[6]
9	Ferulicacid	Phenol	194.18	[6]
10	Methylvanillate	Phenol	182.17	[5]
11	Vannilin	Phenol	152.15	[5]
12	Sinapaldehyde	Phenol	208.07	[5]
13	p-Coumarylpentose	Phenol	913.68	[5]
14	p-Coumaricacid	Phenol	164.04	[5]
15	Sinapicacid	Phenol	224.21	[5]
16	Trans-Ferulicacid	Phenol	194.18	[5]
17	Cis-Ferulicacid	Phenol	194.18	[5]
18	6-C-glucosyl-8-C-arabinosylapigenin	Flavonoid	564.5	[5]
19	Apigenin	Flavonoid	270.05	[5]

Molecular weights given in the table are from the Pubchem database)[21]

Table 6: Phytochemicals of foxtail millet.

Sl. No	Name of the compound	Phytochemical	Molecular weight (g/mol)	Reference
1	Xanthophyll	Carotenoids	586.9	[29]
2	Zeaxanthin	Carotenoids	568.88	[29]
3	Vanillicacid	Phenols	338.2	[16]
4	Protecatechulicaldehyde	Phenols	138.2	[16]
5	p-Hydroxybenzoicacid	Phenols	138.12	[16]
5	p-Hydroxybenzaldehyde	Phenols	122.12	[16]
6	2-Methylisocitricacid	Phenols	206.15	[16]
7	Vanillicacid	Phenols	168.14	[16]
8	Syringicacid	Phenols	198.17	[16]
9	cis-p-Coumaricacid	Phenols	164.16	[16]
10	trans-p-Coumaricacid	Phenols	326.3	[16]
11	Ferulictruxillicacid	Phenols	296.3	[16]
12	Ferulicacid	Phenols	194.18	[16]
13	Sinapicacid	Phenols	224.21	[16]
14	Protecatechulicacid	Phenols	154.12	[16]
15	Homocitricacid	Phenols	206.15	[16]
16	2-Methylisocitricacid	Phenols	206.15	[16]
17	Caffeicacid	Phenols	180.16	[16]
18	N,N′,N″-diferuloylspermidine-Dihexoside	Phenols	673.8	[16]
19	Caffeoylspermidine	Phenols	142.5	[16]
20	Apigenin	Phenols	564.5	[16]
21	Kaempferol	Phenols	286.24	[16]
22	N′-caffeoyl-N′-feruloylspermidine	Phenols	483.6	[16]
23	Di-p-coumaroylspermidine	Phenols	437.23	[16]

Molecular weights given in the table are from Pubchem database)[21]

PHARMACOLOGICAL ACTIVITY OF MINOR MILLET PHYTOCHEMICALS

Phytochemical profile of minor millets is composed of a diverse set of compounds including polyphenols, flavonoids, phenolic acids, and their respective derivatives. The ability of these compounds to avail different therapeutic attributes has been explored by many researchers in recent years. Detailed accounts on phytochemical derivatives capable of exhibiting health benefits are discussed below. A summary of all therapeutic attributes of the respective phytochemicals are listed in Table 7. Antioxidants are important groups of chemical compounds that play a vital roles in neutralizing free radicals through oxidation or reduction reaction.[17] The ability of antioxidants to inhibit the production of free radicals plays important role in controlling the progression of various diseases including degenerative diseases.[25] Such antioxidant activity is exhibited by a wide variety of phytochemicals, mainly phenolic acids, flavonoids, and polyphenols. Due to the growing interest in natural antioxidants, scientists have investigated various minor millets' phytochemicals with antioxidant properties that can be used to treat human ailments. Phytochemicals present in foxtail millet methanol extract have shown significantly higher free radical scavenging activity in DPPH (2,20-diphenyl-1-picrylhydrazyl) assay system.[30] Potential antioxidants extracted from barnyard millet have shown significant DPPH activity and significant 2,2′-Azinobis activity.[31] Japanese variety barnyard millet is considered a rich source of phytochemicals containing flavonoids, phenols, and serotonin derivatives screened through Sephadex LH-20 chromatography and preparative HPLC analysis. N-(p-coumaroyl) serotonin was confirmed to exhibit the highest antioxidant activity.[9] *In-vitro* antioxidant assay conducted on little millet extracts examined through DPPH scavenging and β-carotene inhibition assay confirmed its antioxidant activity.[32] Investigations have also reported that germination, steaming, and roasting increases the phytochemicals profile of little millet and thus increase radical scavenging activity when compared to the non-processed little millet samples. HPLC evaluation of such extracts has revealed the presence of derivatives of benzoic acid, aromatic carboxylic acid, and cinnamic acids which are a group of phenolic compounds that are responsible for the antioxidant activity of little millet.[6] Methanol extracts of Kodo millet flours are a rich source of phytochemicals containing flavonoids and phenols. Electron Spin Resonance (ESR) spectroscopic studies of kodo millet extracts have confirmed the free-radical quenching ability, thus confirming the antioxidant activity.[19] Porso millet extract were also reported to show potential antioxidant activity with the presence of significant amounts of phytochemicals. Porso millet extracts examined through DPPH assay are reported to show free radical scavenging activity.[33] Phytochemicals isolated from all five minor millet methanolic extracts are reported to possess promising free radical quenching ability. Antioxidant activity is known to play a key role in regulating oxidation reactions that damage cells or organisms. Antioxidant activity exhibited by minor millets gives strong grounds for further investigation for using these phytochemicals present in minormillets in the treatment of various diseases. Antimicrobial activity is also a well-known therapeutic property exhibited by minor millet extracts. With growing concern against microbial infections, investigations have been made to screen the antimicrobial potential of minor millets with the aim of inhibiting the infection. Methanolic extracts of Kodo millet with the presence of polyphenols, whose antagonistic spectra has confirmed inhibition against four bacterial strains viz. *Leuconostoc mesenteroides, Enterococcus faecalis, Bacillus cereus, and Staphylococcus aureus* proving its antibacterial activity.[34] *In-vitro* antibacterial assays of little millet extracts screened against bacterial strains including *Pseudomonas aeruginosa* (MTCC1688), *Bacillus megaterium* (MTCC-428), *Escherichia coli* (MTCC443)and *Staphylococcus aureus* (MTCC 96), has confirmed that phytochemicals are responsible for inhibition activity of micro-organisms and therefore can be potential source of novel antibacterial drugs.[32]

Increase in blood glucose levels has become a major health concern in recent years due to its associated complications like hyperglycemia and diabetes. Although several drugs are effective in treating this disease, researchers are engaged in understanding natural compounds for their effect in regulating sugar level. Investigations have explored minor millet phytochemicals for understanding its hypoglycemic activity. Alpha-amylase and glucosidase are the two key digestive enzymes responsible for the degradation of glucose, causing an increase in postprandial glucose levels.[35] Barnyard millet phytochemicals mainly showing the presence of phenolic compounds including apigenin, kaempferol, formononetin, dihydroquercetin, and catechin have been revealed to exhibit antidiabetic activity. Methanol extract of barnyard millet variety is capable of inhibiting the digestive enzymes with the lowest IC_{50} values, thus indicating the regulation of type 2 diabetes.[31] Processing of barnyard millet, foxtail millet, and porso millet varieties by germination enhances the content of phenolic compounds in their extracts and has potential in enzyme inhibitory activity post processing.[6] IC_{50} values reported for post-germinated millet extracts are much lower than compared to non-processed ones, thus indicating the hypoglycemic ability of the millets in regulating glucose levels.[36] Phenolic compounds present in 70% ethanol extract of porso millet and foxtail millet can potentially inhibit α-amylase and glucosidase activity, showcasing the decrease in glucose levels these results were confirmed by lower IC_{50} values which indicate the highest inhibition.[37] Reports also indicate that diabetes-induced Male Wistar albino rats administered with ethanol and aqueous extracts of kodo millet containing phenolic compounds showed a dose-dependent fall in fasting blood glucose levels and a significant increase in insulin levels after 15 days of treatment period.[38] Apart from α-Amylase and glucosidase, protein glycation plays a vital role in the progression of diabetes-related complications; therefore protein glycation inhibition is one of the key strategies in regulating glucose levels. The kodo millet extract treatment is also effective in regulating liver glycogen and glycolated hemoglobin.[38] *P*-coumaric and chlorogenic acids are the major phenolic acids in barnyard millet reported to as capable of 68.3% inhibition of protein glycation, thereby reduces formation of protein aggregates and also protects glycoxidation induced protein conformational changes. Therefore, the potential utility of barnyard millet can regulate protein glycation associated with diabetic complications.[10] Inhibiting abnormal cell proliferation is the most important requirement in cancer treatment, the ability of compounds to inhibitor to stop cell growth is termed as an antiproliferative property. Phytochemicals are well-studied compounds identified as antiproliferative agents, several phytochemical derivatives, and compounds isolated from different plant sources are known to inhibit cell proliferation. Minor millet phytochemicals are also an exception where the compounds present in their extracts also contribute in inhibiting cell growth. Phenolic compounds like syringic acid, chlorogenic acid, q-coumaric acid, carotenoids like xanthophyll and zeaxanthin, ferulic acid and caffeic acid present in foxtail millet are capable of inhibiting HepG2 and MDA cell proliferation. The antiproliferative activity can be screened by MTT assay where low IC_{50} values indicate higher inhibition rates.[29] Polyphenols isolated from foxtail millet bran can inhibit growth and induce apoptosis of human colorectal cancer HCT-116 cells and in HCT-116 cells bearing nude mice. The polyphenols mainly induce pro-apoptotic activity due to activation of mitochondria-mediated intrinsic pathway and blockage of NF-κB signaling pathway. Reports indicated that foxtail millet derived polyphenols can act as natural antiproliferative agents against colon cancer.[39] Kodo millet extracts with p-coumaric acid and ferulic acid can inhibit HT-29 colorectal cancer (CRC) cells in a dose-dependent manner where extract at a concentration of 0.5 mg/mL inhibits cell proliferation nearly100% after 24 hr of incubation and throughout the incubation period of 96 hr.[5] Ferulic acid and chlorogenic present in porso millet extracts can inhibit MDA cells and HepG2 cells whose analysis can be done by methylene blue assay.[14] Phenolic extracts of kodo millet, little millet, porso millet, and foxtail millet inhibited HT-29 cell proliferation in the range of 28-100%.[5]

Inflammation is a prominent event of any disease and controlling or regulating inflammation-associated complications is always been at ask while treating chronic diseases like asthma, cancer, hypersensitivity, etc. Commercial anti-inflammatory drugs that are currently used mainly aim at interleukins and interferons which play key roles in inflammation. Phytochemicals derived from certain minor millets have exhibited potential pro-inflammatory and anti-inflammatory activities. Polyphenols present in foxtail millet bran extracts restrain the level of various proinflammatory cytokines (IL-1β, IL-6, and IL-8), and upregulates the expression of inflammatory cytokines(IL-10) by inhibiting the nuclear factor-kappaB (NFκB)-p65 nuclear translocation in HT-29 cells. This property of bound polyphenols of foxtail millet helps in treating inflammation. The ability of polyphenols to inhibit pro-inflammatory cytokines can be examined by monitoring miR-149 expression, where over expressed miR-149 by ROS accumulation and promotes anti-inflammatory activities.[39] Ethanol extract of porso millet, barnyard millet, and foxtail millet caused down-regulation of iNOS- and COX-2 specific transcript and protein expression levels, as well as proinflammatory cytokine genes (IL-1β1β, IL-6, and TNF-α) expression levels in LPS-stimulated RAW264.7 cells.[12]

ROLE OF MINOR MILLET PHYTOCHEMICALS IN REGULATING LIPIDL EVELS

Increase in serum lipid concentration is associated with several risk factors causing hyperlipidemia and obesity.[41] Elevated level of low-density lipoproteins in serum leads to blockage in blood vessels causing cardiovascular complications. Further risk factors involve accumulation of fat in adipocytes, also causing fatty liver and also leading to obesity.[42] Consumption of high-fat diet and lesser energy expenditure is often identified as a major risk factor. Treatment for lipid-associated disorders mainly involves the use of cholesterol lowering drugs like statins *viz.* atrovastin, fluvastin, pravastin and lovastin.[43] However, several complications associated with statin therapy has led to the search of new therapeutic agents to minimize the side effects associated with the drugs. Phytochemicals isolated from various plant species have the potential in regulating lipid levels. Minor millet phytochemicals are also identified to

Table 7: Pharmacological effects of minor millet phytochemicals.

Sl. No	Name of the compound	Phytochemical	Molecular weight (g/mol)	Reference
1	Methyl vanillate	Phenol	182.17	[40]
2	Vannilin	Phenol	152.15	[40]
3	Sinapaldehyde	Phenol	208.07	[40]
4	p-Coumaryl pentose	Phenol	913.68	[40]
5	p-Coumaric acid	Phenol	164.04	[40]
6	Sinapic acid	Phenol	224.21	[40]
7	Trans-Ferulic acid	Phenol	194.18	[40]
8	Cis-Ferulic acid	Phenol	194.18	[40]
9	6-C-glucosyl-8-C-arabinosyl apigenin	Flavonoid	564.5	[40]
10	Apigenin	Flavonoid	270.05	[40]

be effective in lowering lipid concentrations. A detailed note on millet phytochemicals capable of altering lipid levels are discussed below.

Lipid peroxidation is an important factor causing the release of free radicals from lipids, leading to cell damage. Therefore, inhibiting lipid peroxidation is an important factor in regulating lipid degradation. Little millet and foxtail millet containing ferulic acid as their prominent compound is capable of carrying out lipid peroxidation in a liposome system.[44] Kodo millet extracts containing mainly phenolic acids are capable of lowering serum triglycerides, total cholesterol, very low-density lipoprotein (LDL), and increase in high density lipoproteins (HDL).[38] Decrease in low density lipoprotein is akey targetin lipid associated disorders; therefore phytochemicals isolated from millet extracts might be potential in lowering lipid levels. As prevention of LDL oxidation is important step, phenolic extracts of kodo millet containing caffeic acid, p-coumaric acid and ferulic acid are capable of inhibiting copper-catalyzed human LDL cholesterol oxidation in *in-vitro* condition.[44] Copper can catalyze oxidation of unsaturated fatty acids molecules present in cholesterol. Inhibition of cholesterol oxidation of millet phecolic compounds could account in chelation of cupricions and also the scavenging of free radical species.[44] Methanol extract of foxtail millet can lower lipid accumulation in HepG2 cells by lowering levels of triglycerides and total cholesterol. Genes associated with hepatic lipid metabolism (FAS, SREBP-1C, and HMGCR) are reported to be down-regulated in high fat-fed ratfed along with millet supplementation.[16]

ACKNOWLEDGEMENT

The study was carried out solely by the authors of the paper.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MMs: Minor millets; **GC-MS:** Gas chromatography and mass spectrophotometry; **HPLC:** High-performance liquid chromatography.

REFERENCES

1. De Wet JMJ, Brink DE, Rao KEP, Mengesha MH. Diversity in kodo millet, Paspalum scrobiculatum. Econ Bot. 1983 Apr;37(2):159-63. doi: 10.1007/BF02858779.
2. Nagarajan L, Smale M, Glewwe P. Determinants of millet diversity at the household-farm and village-community levels in the drylands of India: the role of local seed systems. Agric Econ. 2007 Mar;36(2):157-67. doi: 10.1111/j.1574-0862.2007.00195.x.
3. Nisar B, Sultan A, Rubab SL. Comparison of medicinally important natural products versus synthetic drugs-a short commentary. Nat Prod Chem Res. 2018;06(2):308. doi: 10.4172/2329-6836.1000308.
4. Biswas S, Banerjee N, Basak P. Adverse effects of the toxic industrial dye malachite green on the antioxidant and antimicrobial properties of Allium cepa L. Plant Sci Today. 2022 Apr 1;9(2):236-42. doi: 10.14719/pst.1339.
5. Chandrasekara A, Shahidi F. Bioactivities and antiradical properties of millet grains and hulls. J Agric Food Chem. 2011 Sep 14;59(17):9563-71. doi: 10.1021/jf201849d, PMID 21770397.
6. Pradeep SR, Guha M. Effect of processing methods on the nutraceutical and antioxidant properties of little millet (Panicum sumatrense) extracts. Food Chem. 2011 Jun 15;126(4):1643-7. doi: 10.1016/j.foodchem.2010.12.047, PMID 25213939.
7. Deshpande SS, Mohapatra D, Tripathi MK, Sadvatha RH. Kodo millet nutritional value and utilization in Indian foods. J Grain Process Storage. 2015 Jul;2(2):16-23.
8. Sharma S, Saxena DC, Riar CS. Using combined optimization, GC–MS and analytical technique to analyze the germination effect on phenolics, dietary fibers, minerals and GABA contents of Kodo millet (Paspalum scrobiculatum). Food Chem. 2017 Oct 15;233:20-8. doi: 10.1016/j.foodchem.2017.04.099, PMID 28530567.
9. Watanabe M. Antioxidative phenolic compounds from Japanese barnyard millet (*Echinochloa utilis*) grains. J Agric Food Chem. 1999;47(11):4500-5. doi: 10.1021/jf990498s, PMID 10552841.
10. Anis MA, Sreerama YN. Inhibition of protein glycoxidation and advanced glycation end-product formation by barnyard millet (*Echinochloa frumentacea*) phenolics. Food Chem. 2020;315:126265. doi: 10.1016/j.foodchem.2020.126265, PMID 32014668.
11. Das AK, Singh V. Antioxidative free and bound phenolic constituents in botanical fractions of Indian specialty maize (*Zea mays* L.) genotypes. Food Chem. 2016 Jun 15;201:298-306. doi: 10.1016/j.foodchem.2016.01.099, PMID 26868580.
12. Lee JY, Jun DY, Yoon YH, Ko JY, Woo KS, Woo MH, *et al*. Anti-inflammatory effect of flavonoids kaempferol and biochanin A-enriched extract of barnyard millet (*Echinochloa crus-galli* var. frumentacea) grains in LPS-stimulated RAW264. 7 cells. J Life Sci. 2014;24(11):1157-67. doi: 10.5352/JLS.2014.24.11.1157.
13. Murugan S, Shanmugam A, Manoharan L, Sundaramoorthy S, Gunasekaran S, Arunachalam S, *et al*. Antioxidant activity of aqueous and methanol extract of barnyard millet. Res J Pharm Technol. 2016;9(3):262-6. doi: 10.5958/0974-360X.2016.00048.2.
14. Zhang L, Liu R, Niu W. Phytochemical and antiproliferative activity of proso millet. PLOS ONE. 2014 Aug 6;9(8):e104058. doi: 10.1371/journal.pone.0104058, PMID 25098952.
15. Saleh ASM, Zhang Q, Chen J, Shen Q. Millet grains: Nutritional quality, processing, and potential health benefits. Compr Rev Food Sci Food Saf. 2013 May;12(3):281-95. doi: 10.1111/1541-4337.12012.
16. Xiang J, Zhang M, Apea-Bah FB, Beta T. Hydroxycinnamic acid amide (HCAA) derivatives, flavonoid C-glycosides, phenolic acids and antioxidant properties of foxtail millet. Food Chem. 2019 Oct 15;295:214-23. doi: 10.1016/j.foodchem.2019.05.058, PMID 31174752.
17. Shahidi F, Zhong Y. Measurement of antioxidant activity in food and biological systems. ACS Symposium Series. 2007:36-66. doi: 10.1021/bk-2007-0956.ch004.
18. Tsuzuki W, Komba S, Kotake-Nara E, Aoyagi M, Mogushi H, Kawahara S, *et al*. The unique compositions of steryl ferulates in foxtail millet, barnyard millet and naked barley. J Cereal Sci. 2018 May 1;81:153-60. doi: 10.1016/j.jcs.2018.04.006.
19. Hegde PS, Chandra TS. ESR spectroscopic study reveals higher free radical quenching potential in kodo millet () compared to other millets. Food Chem. 2005 Aug 1;92(1):177-82. doi: 10.1016/j.foodchem.2004.08.002.
20. Patil RB, Vijayalakshmi KG, Vijayalakshmi D. Physical, functional, nutritional, phytochemical and antioxidant properties of kodo millet (*Paspalum scrobiculatum*). J Pharmacogn Phytochem. 2020;9(5):2390-3.
21. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S *et al*. PubChem in 2021: New data content and improved web interfaces. Nucleic Acids Res. 2021 Jan 8;49(D1):D1388-95. doi: 10.1093/nar/gkaa971, PMID 33151290.
22. Amadou I, Gounga ME, Le GW. Millets: Nutritional composition, some health benefits and processing-A review. Emirates J Food Agric. 2013 May 1:501-8.
23. Sharma S, Saxena DC, Riar CS. Analysing the effect of germination on phenolics, dietary fibres, minerals and γ-amino butyric acid contents of barnyard millet (*Echinochloa frumentaceae*). Food Biosci. 2016 Mar 1;13:60-8. doi: 10.1016/j.fbio.2015.12.007.
24. Kom YD. *In vitro* antioxidant activity of barnyard millet (*Echinochola esculenta* (A. Braun) H. Scholz) and proso millet (*Panicum miliaceum* L.). *In vitro* Antioxidant Activity of Barnyard Millet (*Echinochola esculenta* (A. Braun) H. Scholz) and Proso Millet (*Panicum miliaceum* L.) (February 5, 2020). Proceedings of the international conference on drug discovery (ICDD); 2020.
25. Sen S, Chakraborty R. The role of antioxidants in human health. ACS Symposium Series. 2011:(1-37). doi: 10.1021/bk-2011-1083.ch001.

26. Dong W, An CB, Fan W, Li H, Zhao X. Stable isotopic detection of manual intervention among the faunal assemblage from a Majiayao site in NW China. Radiocarbon. 2016 Jun;58(2):311-21. doi: 10.1017/RDC.2015.6.
27. Zhu Y, Chu J, Lu Z, Lv F, Bie X, Zhang C, *et al*. Physicochemical and functional properties of dietary fiber from foxtail millet (*Setaria italica*) bran. J Cereal Sci. 2018 Jan 1;79:456-61. doi: 10.1016/j.jcs.2017.12.011.
28. Sharma N, Goyal SK, Alam T, Fatma S, Niranjan K. Effect of germination on the functional and moisture sorption properties of high–pressure-processed foxtail millet grain flour. Food Bioprocess Technol. 2018 Jan;11(1):209-22. doi: 10.1007/s11947-017-2007-z.
29. Zhang LZ, Liu RH. Phenolic and carotenoid profiles and antiproliferative activity of foxtail millet. Food Chem. 2015 May 1;174:495-501. doi: 10.1016/j.foodchem.2014.09.089, PMID 25529711.
30. Suma PF, Urooj A. Antioxidant activity of extracts from foxtail millet (*Setaria italica*). J Food Sci Technol. 2012 Aug;49(4):500-4. doi: 10.1007/s13197-011-0300-9, PMID 23904660.
31. Ofosu FK, Elahi F, Daliri EB, Chelliah R, Ham HJ, Kim JH, *et al*. Phenolic profile, antioxidant, and antidiabetic potential exerted by millet grain varieties. Antioxidants (Basel). 2020 Mar;9(3):254. doi: 10.3390/antiox9030254, PMID 32245008.
32. Mehta JP, Vadia SH. *In-vitro* antioxidant activity and antibacterial assay of minor millet extracts. J Chem Pharm Res. 2014;6(7):2343.
33. Kim J, Hyun TK, Kim M. Anti-oxidative activities of sorghum, foxtail millet and proso millet extracts. Afr J Biotechnol. 2010;9(18):2683-90.
34. Sharma S, Sharma N, Handa S, Pathania S. Evaluation of health potential of nutritionally enriched Kodo millet (Eleusine coracana) grown in Himachal Pradesh, India. Food Chem. 2017 Jan 1;214:162-8. doi: 10.1016/j.foodchem.2016.07.086, PMID 27507461.
35. Mcdougall GJ, Stewart D. The inhibitory effects of berry polyphenols on digestive enzymes. BioFactors. 2005;23(4):189-95. doi: 10.1002/biof.5520230403, PMID 16498205.
36. Pradeep PM, Sreerama YN. Impact of processing on the phenolic profiles of small millets: Evaluation of their antioxidant and enzyme inhibitory properties associated with hyperglycemia. Food Chem. 2015 Feb 15;169:455-63. doi: 10.1016/j.foodchem.2014.08.010, PMID 25236251.
37. Kim JS, Hyun TK, Kim MJ. The inhibitory effects of ethanol extracts from sorghum, foxtail millet and proso millet on α-glucosidase and α-amylase activities. Food Chem. 2011 Feb 15;124(4):1647-51. doi: 10.1016/j.foodchem.2010.08.020.
38. Jain S, Bhatia G, Barik R, Kumar P, Jain A, Dixit VK. Antidiabetic activity of *Paspalum scrobiculatum* Linn. in alloxan induced diabetic rats. J Ethnopharmacol. 2010 Feb 3;127(2):325-8. doi: 10.1016/j.jep.2009.10.038, PMID 19900528.
39. Shi J, Shan S, Li Z, Li H, Li X, Li Z. Bound polyphenol from foxtail millet bran induces apoptosis in HCT-116 cell through ROS generation. J Funct Foods. 2015 Aug 1;17:958-68. doi: 10.1016/j.jff.2015.06.049.
40. Chandrasekara A, Shahidi F. Antiproliferative potential and DNA scission inhibitory activity of phenolics from whole millet grains. J Funct Foods. 2011 Jul 1;3(3):159-70. doi: 10.1016/j.jff.2011.03.008.
41. Ginsberg HN, Zhang YL, Hernandez-Ono A. Regulation of plasma triglycerides in insulin resistance and diabetes. Arch Med Res. 2005 May 1;36(3):232-40. doi: 10.1016/j.arcmed.2005.01.005, PMID 15925013.
42. Snel M, Jonker JT, Schoones J, Lamb H, De Roos A, Pijl H, *et al*. Ectopic fat and insulin resistance: Pathophysiology and effect of diet and lifestyle interventions. Int J Endocrinol. 2012 Oct;2012:983814. doi: 10.1155/2012/983814, PMID 22675355.
43. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the primo study. Cardiovasc Drugs Ther. 2005 Dec;19(6):403-14. doi: 10.1007/s10557-005-5686-z, PMID 16453090.
44. Chandrasekara A, Shahidi F. Content of insoluble bound phenolics in millets and their contribution to antioxidant capacity. J Agric Food Chem. 2010 Jun 9;58(11):6706-14. doi: 10.1021/jf100868b, PMID 20465288.

GRAPHICAL ABSTRACT

SUMMARY

With changing lifestyle and unhealthy food habits, human life has took a considerable graph in emerging life-threatening diseases. Therefore the demand for discovery of new drugs and therapeutic agents is never-ending. Even though chemically synthesized drugs are efficient in treating several medical conditions, side effects associated with them makes ways for several drawbacks. Phytochemicals has been an emerging field in finding cure for such diseases. Phytochemicals isolated from various plants have proven to possess numerous therapeutic properties including anti-bacterial, anti-diabetic, anti-inflammatory, anti-cancer, anti-inflammatory etc. Minor millets being one of the under-utilized groups of cereals, whose consumption rates are decreased over the years, are now known to avail several health benefits due to the presence of potential phytochemicals. Minormillet phytochemicals discussed in the current review are reported to showcase the major health benefits in crude methanol and ethanol extracts of minor millets. The compounds identified from such extracts can be further isolated for evaluating their activity in in-vivo conditions. Current data will be useful in previewing all the phytochemicals that are present in minor millets and also provides insight into all the potential health benefits exhibited by the compounds. A detailed account on the ability of minor millets in regulating lipids helps in further research for identifying new phytochemicals that have the ability to manage lipid concentration by inhibiting specific target proteins. Thus the current data can become useful content for carrying out further research with a special focus on therapeutics of minor millet phytochemicals.

Cite this article: Pujari N, Hoskeri JH. Minor Millet Phytochemicals and their Pharmacological Potentials. Pharmacog Rev. 2022;16(32):100-6.