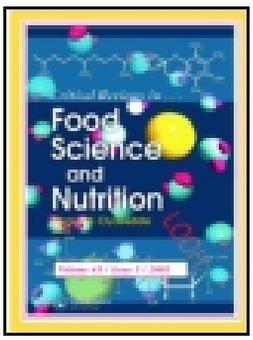

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Abdul Majid & Poornima Priyadarshini C G (2019): Millet derived bioactive peptides: A review on their functional properties and health benefits, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2019.1686342

To link to this article: https://doi.org/10.1080/10408398.2019.1686342

Published online: 05 Nov 2019.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2019.1686342

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REVIEW

Millet derived bioactive peptides: A review on their functional properties and health benefits

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ABSTRACT

Millets, cereals and grains play an important role in providing adequate nutrition and as well shown to possess beneficial effects on lifestyle disorders. Several studies on millet seed proteins and their hydrolysates, have demonstrated their physiological role in the prevention of chronic diseases by acting on various molecular targets. In recent years, the importance of food derived bioactive peptides is surging at an exponential rate in both nutraceutical and pharmaceutical research. A considerable number of earlier reviews have discussed their role in improving the human health. However, a concise review on millet-derived peptides and their purported role in human health is still lacking. Thus, this review provides an extensive survey of key bioactive millet peptides (BAMPs) reported till date in a succinct form. BAMPs are derived through enzymatic hydrolysis of the seed proteins and are known to perform several regulatory functions in vitro and in vivo. Several *in silico* and in vitro studies have demonstrated the antimicrobial, antioxidant, antihypertensive, anticancer and antidiabetic properties of BAMPs. Even though, the biological application of these peptides profoundly depends on the size and structure, the absorption in target tissues and bioavailability also play a critical role. Thus, the aim of this review is to discuss and summarize several key BAMPs from various millets reported so far, focusing on their proposed multifaceted biochemical activity, production, purification and mechanism of action. In addition, some of the key parameters for the successful delivery and bioavailability of these peptides are also highlighted. Nevertheless, in-depth investigations on the in vivo mode of action of BAMPs crucial in future to validate and translate these observed effects to human health benefits.

KEYWORDS

Bioactive millet peptides (BAMPs); antimicrobial: anti-inflammatory; antihypertensive; anticancer; antidiabetic

Introduction

Dietary quality of food is an important criterion in improving health as well in the prevention of many chronic diseases, including malnutrition. Millets are highly nutritious but vastly ignored as a main source of food primarily due to lack of awareness. However, increasing research on millets showing beneficial effects on health, they have gained significant importance in the field of biomedical research (Rao, Nagasampige, and Ravikiran 2011). Most importantly, millets have additional agronomical benefits due to their drought-resistant characteristics, short growing periods and ability to grow under dry and high temperature conditions. They are also easier to process and exhibit excellent resistance to pests and diseases. As per a consensus data acquired in 2013, the total world production of millet grains was 762,712 metric tons and India ranks the top, contributing to 43.85% of overall production with an yearly yield of 334,500 tons (Chandel et al. 2014) .

Millets are small-seeded grasses, cultivated around the world as grains or cereal crops. Millets are divided into two types, namely, major and minor millets. Pearl millet (*Pennisetum glaucum*), Proso or white millet (*Panicum miliaceum*), Foxtail millet (*Setaria italic*), and Finger millet (*Eleusine coracana*) are the major millets. Whereas, Barnyard millet (*Echinochloa spp.*), little millet (*Panicum sumatrense*), Guinea millet (*Brachiaria deflexa*), Browntop millet (*Urochloa ramose*), Kodo millet (*Paspalum scrobiculatum*), and Sorghum (Sorghum spp.) are minor millets (Hunt et al. 2008; Bandyopadhyay, Muthamilarasan, and Prasad 2017).

Millets are minuscule, round in shape and their high nutrient content is contributed by carbohydrates (60–70%), proteins (7–11%), crude fiber (2–7%) and fat (1.5–5%). Besides, millets are gluten free and are rich in vitamin B, iron, calcium, potassium, zinc and magnesium. Lately, there has been a progressive interest towards millets as it contains essential nutrients and bioactive components enriched with the health-promoting activities. Hence, millets could be exploited as nutraceuticals and used in therapeutic applications towards chronic diseases such as obesity, cardiovascular diseases, cancer and diabetes (Chandrasekara and Shahidi 2011; Chandra et al. 2016; Kumar et al. 2016; Guo et al. 2018). It has also been reported that millets, when

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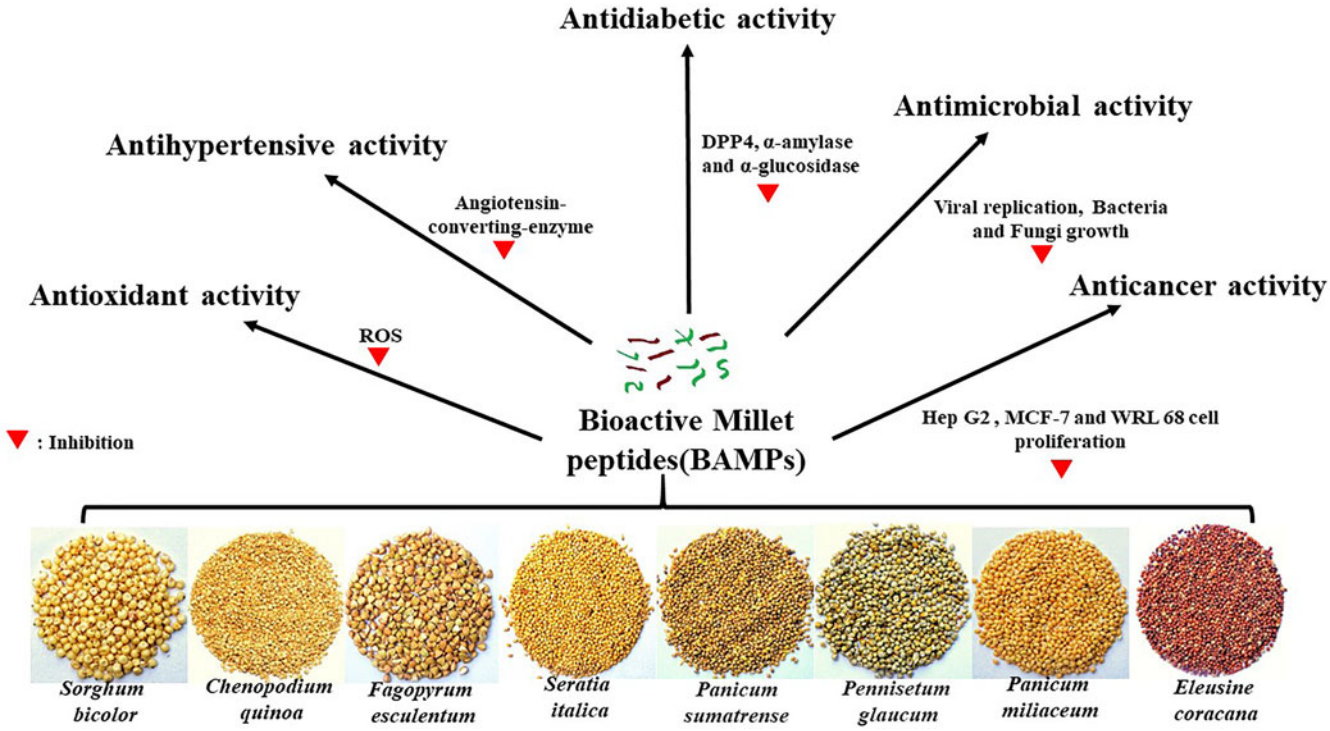

Figure 1. Health promoting biological activities of bioactive millet peptides (BAMPs).

compared to other cereals, are known to have lower starch and protein digestibility rates. This hypoglycemic property has been attributed to the various factors such as polyphenols, fibers, starch-protein-lipid interactions and intrinsic structural properties of starch present in millets (Annor et al. 2017).

Millet proteins and bioactive peptides

Typical millet seed protein contains fractions of albumin, globulin, cross-linked prolamin, β-prolamin and glutelin. However, the relative levels of these proteins vary depending on the variety of millets (Virupaksha, Geeta, and Dasasetty 1975). Further, amino acid analysis of millet proteins have revealed the presence of high quantity of essential amino acids including sulfur containing amino acids such as cysteine and methionine (Geervani and Eggum 1989). Plant peptides, in general, are protein fragments smaller than 10 kDa (Farrokhi, Whitelegge, and Brusslan 2008). These peptides may exist naturally or are derived from their native/precursor protein during hydrolysis by digestive or proteolytic enzymes. Bioactive peptides (BAPs) are such byproducts from various biological sources with a positive influence on body functions or conditions ultimately influencing the health of an individual. In this direction, BAMPs have been identified to exert distinct biochemical effects on human health such as antimicrobial, antioxidant, antihypertensive, ACE-inhibitory, antiproliferative/anticancer and antidiabetic effect (Haque and Chand 2008; Chakrabarti, Jahandideh, and Wu 2014; Cicero, Fogacci, and Colletti 2017; Li et al. 2018; Ganguly, Sharma, and Majumder 2019) (Figure 1). In the review we focus on BAMPs derived from seeds of sorghum bicolor, foxtail, buckwheat, finger millet, pearl millet, chia and quinoa in detail for their biological activities reported so far (Table 1).

Antimicrobial activity

The recent emergence of drug-resistant bacterial and viral strains entails the need for exploratory research on naturally occurring antimicrobial/viral agents including proteins and their synthetic chemical derivatives with a potential promise for clinical use. In this direction, a study by Camargo et al. revealed the presence of anti-viral peptides from jower. Jower derived 2 kDa peptide showed a strong inhibition the replication of bovine herpes virus (BHV), herpes simplex virus type 1 (HSV-1) and a weak activity against poliovirus type 1. Further, the peptides were also shown to inhibit the spread of HSV-1 infection along with a prophylactic effect against secondary infection in vitro (Camargo Filho et al. 2008). A 4 kDa peptide derived from Buckwheat was shown to inhibit HIV-1 reverse transcriptase activity in vitro with an IC50 of 5.5 μM. In addition, buckwheat derived peptides also showed an antifungal activity against *Mycosphaerella arachidicola and Fusarium oxysporum* with an IC50 of 40 μM and 35 μM, respectively. Glycine and cysteine rich sequences present in these peptides was responsible for this anti-fungal activity (Leung and Ng 2007). Such sequence similarities is observed in number of other plant proteins and hydrolysates that possess anti-fungal/antibacterial activity (Broekaert et al. 1992; Fujimura et al. 2003; Egorov et al. 2005). Fujimura et al has identified two novel antimicrobial peptides from Buckwheat, Fa-AMP1 and Fa-AMP2 that showed a broad spectrum of anti-microbial activity against gram-positive (*clavibacter michiganensis and curtobacteruim faccumfaciens)*, gram-negative bacteria *(Agrobacterium*

Table 1. Millet derived BAMPs and their biological activities.

Source	Precursor Protein	Peptide sequence/ hydrolysates	Bioactivity/against	Reference
Jower	Acid-soluble protein	Protein hydrolysates	Antiviral activity/herpes simplex virus type 1 (HSV-1), bovine herpes virus (BHV), Poliovirus type 1	(Camargo Filho et al. 2008)
Jower	Total protein	VAITLTMK and VSKSVLVK	Antioxidant activity	(Agrawal, Joshi, and Gupta 2017)
Finger millet	Total protein	TSSSLNM VRGGLTR and STTVGLGISMRSASVR	Antioxidant	(Agrawal, Joshi, and Gupta 2019)
Buckwheat	Total protein	Protein hydrolysates	Antiviral activity/HIV-1 reverse transcriptase	(Leung and Ng 2007)
Foxtail	Total Protein	Protein hydrolysates	Antifungal activity/*Alternaria alternate*	(Xu et al. 2011)
Buckwheat	Total protein	Protein hydrolysates	Antifungal activity/*Mycosphaerella arachidicola* and *Fusarium oxysporum*	(Leung and Ng 2007)
Buckwheat	Total protein	Protein hydrolysates	Antimicrobial activity/*Agrobacterium rhizogenes* MAFF 210265, *Agrobacterium radiobacter* MAFF 520028, *Clavibacter michiganensis* subsp. michiganensis MAFF 301044, *Fusarium oxysporum* IFO 6384, *Geotrichum candidum* and *Curtobacterium flaccumfaciens* pv. oortii MAFF 301203	(Fujimura et al. 2003)
Finger Millet	Total protein	Protein hydrolysates	Antibacterial effect/*Pseudomonas aeruginosa* (MTCC 424), and *Salmonella entrica* (MTCC 739)	(Bisht, Thapliyal, and Singh 2016)
Foxtail	Total protein	Protein hydrolysates	Antioxidant and Antibacterial activity/*E. coli* ATCC 8099	(Mohamed, Amadou, and Zhou 2012; Amadou et al. 2013)
Pearl millet	Total protein	SDRDLLGPNNQYLPK	Antioxidant effect	(Agrawal, Joshi, and Gupta 2016)
Buckwheat	Total protein	WPL, VPW, VFPW	Antioxidant effect	(Ma et al. 2010)
Foxtail	Total protein	Protein hydrolysates	Antihypertensive effect	(Chen et al. 2017)
Buckwheat	Total protein	DVWY, FQ, VVG, VAE, GPP, DTPF and WTFR	Antihypertensive effect	(Ma et al. 2006; Koyama et al. 2013)
Chia	Total protein	Protein hydrolysates	Antihypertensive effect	(Segura Campos et al. 2013)
Quinoa	Total protein	Protein hydrolysates	ACE-inhibitory activity and radical scavenging activity	(Aluko and Monu 2003)
Buckwheat	Total protein	Protein hydrolysates	Anticancer/antiproliferative against Hep G2 (hepatoma) cells, L1210 (leukemia) cells, breast cancer (MCF-7) cells, liver embryonic WRL 68 cells	(Leung and Ng 2007)
Quinoa	Globulin B	IQAEGGLT, DKDYPK, GEHGSDGNV	Antidiabetic effect	(Vilcacundo, Martínez-Villaluenga, and Hernández-Ledesma 2017)
Buckwheat	Globulin protein	LQAFEPLR and EFLLAGN	Antidiabetic effect	(Wang et al. 2015)

rhizogens, Agrobacterium radiobacter) and against plant pathogenic fungi *(Fusarium oxysporum*, *Geotrichum candidum)* (Fujimura et al. 2003). Further, structural and antimicrobial characteristics of Fa-AMPs indicated that they belong to plant defensin family of peptides. In a study by Xu et al (2011), the authors demonstrated the antifungal activity of foxtail millet derived peptides against different species of fungi, including *Fusarium oxysporum, Trichoderma viride, Botrytis cinerea and Alternaria alternate* (Xu et al. 2011).

Further, proteins/peptides extracted from finger millet, barnyard millet, and proso millet showed varied range of antimicrobial activity against *Pseudomonas aeruginosa* (MTCC 424) and *Salmonella entrica* (MTCC 739) (Bisht, Thapliyal, and Singh 2016). Similarly, three foxtail millet derived peptides FFMp4, FFMp6, and FFMp10 (Amadou et al. 2013) displayed strong antibacterial activity against *E. coli* ATCC 8099. Collectively, these reports demonstrate the prospect of millet derived peptides as promising antimicrobials against virus, bacteria and fungi.

Antioxidant property

Millets are known to contribute to significant supply of antioxidants in the form of phenolic acids and tannins to counteract oxidative stress in vitro and in vivo (Subba Rao and Muralikrishna 2002; Sudhakar et al. 2015; Han et al. 2018). These antioxidant phytochemicals demonstrate radical-quenching activities by their ability to participate in single electron transfer reaction. Nevertheless, there is ample literature available on millet peptides and protein hydrolysates with antioxidant properties in various oxidative reaction systems. Further, presence of abundant of peptidic amino acid residues that can transfer electrons to free radicals at physiological pH, also contribute towards their antioxidant properties (Canabady-Rochelle et al. 2018; Matsui et al. 2018) In this context, a 14-mer peptide SDRLLGPNNQYLPK, isolated from the pearl millet exhibited excellent anti-oxidative property when assessed by ABTS, hydroxyl radical, DPPH and Fe(2^{+}) chelating activity assays (Agrawal, Joshi, and Gupta 2016). Seven bioactive peptides, F2A, F2B, F2C, F2D, F2E, F3A and F3B were isolated from green tender sorghum and characterized for their antioxidant properties. Out of which, F2B (VAITLTMK) and F3A (VSKSVLVK) showed higher antioxidant activity with 74.19% and 77.64% of free radicle inhibition, compared to other peptides (Agrawal, Joshi, and Gupta 2017). Further, the same group has also reported antioxidant activity of bioactive peptides derived from finger millet. Molecular docking studies on these peptides (TSSSLNMAVRGGLTR and

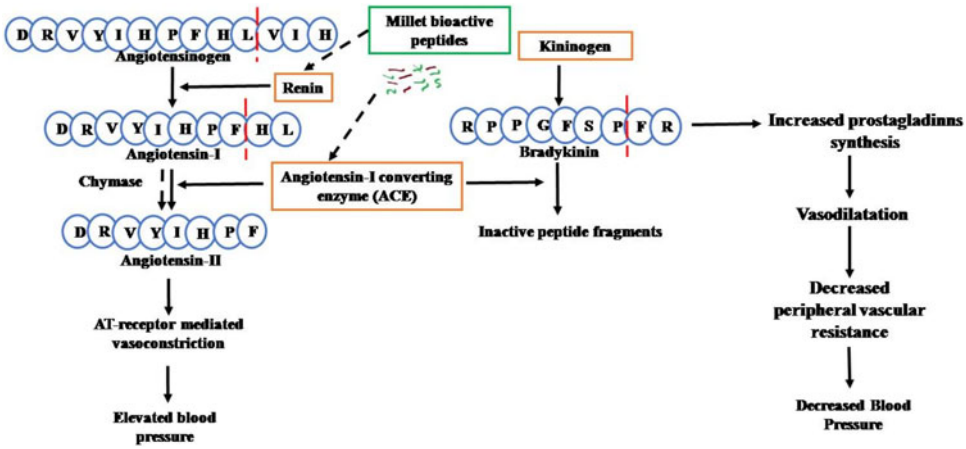

Figure 2. The blood pressure regulating renin-angiotensin system (RAS) pathway showing potential molecular targets (renin and angiotensin-converting enzyme, ACE) for bioactive peptides. Inhibition of renin reduces the possibility of producing angiotensin-II via an ACE-independent chymase-catalyzed reaction.

STTVGLGISMRSASVR) revealed their interaction with free radicals via their serine and threonine residues (Agrawal, Joshi, and Gupta 2019). In addition, foxtail millet derived bioactive peptides, FFMps rich in Tyrosine/Leucine and di, tri and tetrameric peptides containing proline and tryptophan of buckwheat, and protein hydrolysates of quinoa exhibited exhibited significant radical scavenging activity (Aluko and Monu 2003; Ma et al. 2010; Amadou et al. 2013). Taken together, these studies demonstrate the application of the millet derived peptides for reducing oxidative stress and associated diseases and may aid in the development of functional foods or nutraceuticals.

Antihypertensive activity

The renin-angiotensin pathway along with kallikrein-kinnin system (KKS) plays a crucial role in the regulation of the sodium homeostasis and blood pressure. The major substrate of renin–angiotensin system (RAS), angiotensinogen (AGT) is released from the liver and is cleaved by renin, an aspartyl protease to form ANG I. ANG I is further cleaved by angiotensin I-converting enzyme (ACE) at a histidyl residue from the C-terminus to form ANG II, a main RAS vasoactive peptide that later binds to its specific receptors to trigger a broad range of biological actions. As bifunctional enzyme, ACE is also involved in degrading Bradykinin (BK), the central molecule of KKS system, which is generated by the cleavage of kallikrein from kininogen (Figure 2). Liberated BK stimulates formation of nitric oxide (NO) and superoxide leading to vasodilation (Erdos, Tan, and Skidgel 2010; Ceravolo et al. 2014). Thus targeting ACE by various inhibitors may contribute to pleiotropic therapeutic effects in regulating hypertension (Ibrahim 2006). In addition, direct inhibition of renin can also possibly result in fine tuning elevated blood pressure levels as the synthesis of ANG1-I followed by ANG-II is inhibited via an ACE-independent alternative chymase-catalyzed pathway in some tissues (Segall, Covic, and Goldsmith 2007). Several bioactive peptides extracted from various food sources including wheat, oat, barley, rice, milk, eggs, meat, and marine sources have shown to exert antihypertensive activity (Majumder and Wu 2014; Aluko 2015; Lorenzo et al. 2018; Fan, Liao, and Wu 2019; Ganguly, Sharma, and Majumder 2019). In this line, Koyama et al. investigated the blood pressure lowering effect of bioactive peptides from lactic-fermented buckwheat sprouts, in vivo. Six novel bioactive peptides (FQ, VAE, VVG, DVWY, WTFR and FDART) were identified and a single dose administration of these peptides to hypertensive rats resulted in a significant decrease in blood pressure (Koyama et al. 2013). The protein hydrolysates derived from Quinoa also showed the significant inhibition of ACE activity (Aluko and Monu 2003). In another study, chia bioactive peptides derived by controlled protein hydrolysis using Alcalase-Flavourzyme sequential system showed an extensive ACE-inhibitory activity in vitro (Segura Campos et al. 2013). These results show that the inhibition of ACE by millet peptides could effectively act on both RAS and KKS pathways and may be employed to manage hypertension, cardiovascular and chronic diseases.

Anticancer/antiproliferative

Uncontrolled cell proliferation is a major hallmark in development and progression cancer. Hence, vast majority of the anticancer drugs are developed to target the cells with high degree of proliferation and regeneration (DeBerardinis et al. 2008). Several bioactive peptides extracted from various sources have shown to exert anticancer activity (Wu et al. 2014; Díaz-Gómez et al. 2017; Wang et al. 2017). Besides its antifungal activity, Buckwheat derived 4 kDa peptide, was also shown to inhibit the proliferation of Hep G2 (hepatoma), breast cancer (MCF-7) and liver embryonic WRL 68 with an IC (50) of 33 µM, 25 µM, and 37 µM, respectively. However, unlike other known antifungal plant peptides (Ye and Ng 2002), buckwheat derived peptides were devoid of mitogenic response on splenocytes were not able to induce nitric oxide production by macrophages (Leung and Ng 2007). Quinoa-derived peptides such as, LWREGM (F-1), DKDYPK (F-2), RELGEWGI (F-3), DVYSPEAG and IFQEYI were proposed as potential anticancer agents due their antioxidant and chemoprotective activity, since cancer

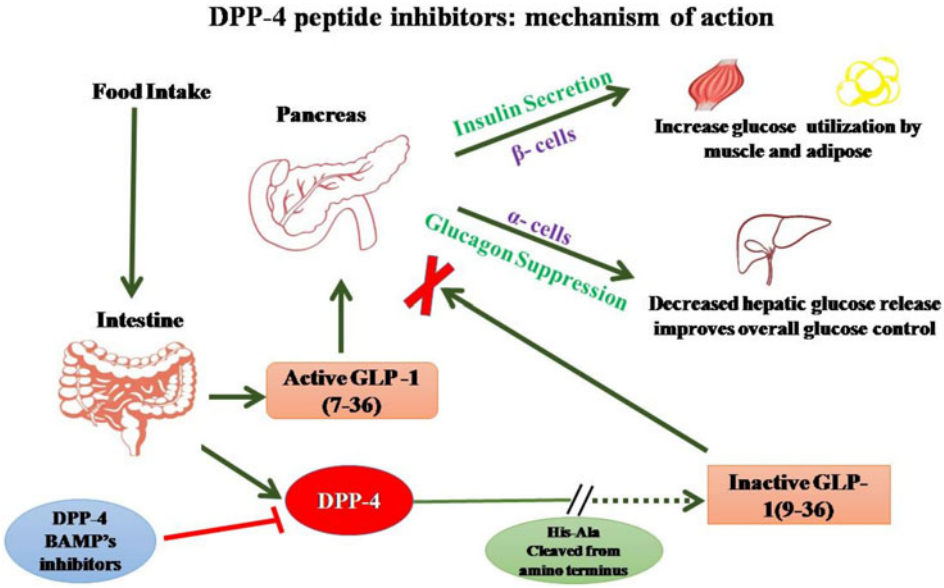

Figure 3. Mechanism of action of dipeptidyl peptidase (DPP4) during diabetes and its inhibition by bioactive peptides.

is tightly linked to reactive oxygen species and oxidative stress (Vilcacundo et al. 2018).

Antidiabetic effects

Diabetes is a metabolic disorder with multiple etiologies, characterized by imbalanced glucose homeostasis due to disturbances in energy metabolism. This results in impaired insulin secretion and insulin resistance (Simmons, Unwin, and Griffin 2010; Whiting et al. 2011). Many drugs are in clinical use to maintain the glucose level, which acts on diverse molecular targets such as, G protein-coupled receptors (GPCR), glucagon receptor (GCGr), free fatty acid receptors 1 (FFAR1), AMP kinase (AMPK), dipeptidyl peptidase 4 (DPP4), peroxisome proliferator activated receptor-γ (PPARγ), α-glucosidase, glycogen phosphorylase (GP), glucose co-transporter-2 (SGLT2), and sodium fructose-1,6-bisphosphatase (FBPase) (Kerru et al. 2018). However, several of them have been reported to have side effects such as weight gain and hypoglycemia.

Bioactive peptides isolated from hydrolysates of plant and animal sources have been reported to have a crucial role in energy homeostasis, insulin signaling and resistance with a promising potential for pharmacological development into therapies for diabetes (Billyard, McTernan, and Kumar 2007; Chakrabarti et al. 2018b). The most accepted treatments in the management of postprandial glucose level is dipeptidyl peptidase 4 inhibitors, glucagon like peptide-1 (GLP-1) analogs, GLP-1 and receptor agonists (Waldrop et al. 2018). DPP4 enzyme in particular, is responsible for the inactivation of GLP-1, which may lead to insulin insensitivity (Figure 3).

In a study on food grains, peptides released from oat, buckwheat, and barley proteins exhibited DPP4 inhibitory activities with varying IC (50) values. The IC (50) values ranged from 0.13 mg/mL (oat) to 8.15 mg/mL (barley). Further, the authors also identified 35 peptides of more than seven residues and LQAFEPLR showed highest IC (50) value of 103.5 μM (Wang et al. 2015).

Further, millet derived hydrolysates and bioactive peptides have been shown to exert favorable satiety and inhibitory effects on DPP4 *in-vitro*. In one such study with quinoa, three bioactive peptides were identified from 11S seed storage globulin B with DPP4, α-amylase and α-glucosidase inhibitory activity in vitro (Vilcacundo, Martínez-Villaluenga, and Hernández-Ledesma 2017). Thus, millets derived BAMPs are a potential source of DPP4 inhibitory peptides targeted at diabetes.

Production of bioactive peptides; current techniques

Dietary proteins *per se* are known to exhibit a wide range of functional and biological activities besides its nutritional property. In addition, fascinatingly, many of these properties are due to the presence of active peptides encrypted within protein molecules. These bioactive peptides are inactive within the sequence of parent protein and becomes active once released. The release of peptides can be achieved by different ways of hydrolysis through digestive enzymes, proteolytic microorganisms, and through enzymes derived from microorganisms or plants (Korhonen and Pihlanto 2003; Harnedy and FitzGerald 2011; Wang et al. 2018). Fermentation using *Lactobacillus spp*. is another most widely used method to the release bioactive peptides from millet protein hydrolysate. Further, this method has other advantages over acid/base digestion, as it does not cause loss of essential amino acid and environmental pollution (Hajfathalian et al. 2018; Raveschot et al. 2018). The functionality and efficacy of these bioactive peptides such as their absorption across the small intestine and their bioavailability in target tissues primarily depend on their size, inherent amino acid composition, sequence and other parameters such as charge, hydrophobicity and rate of hydrolysis (Shen

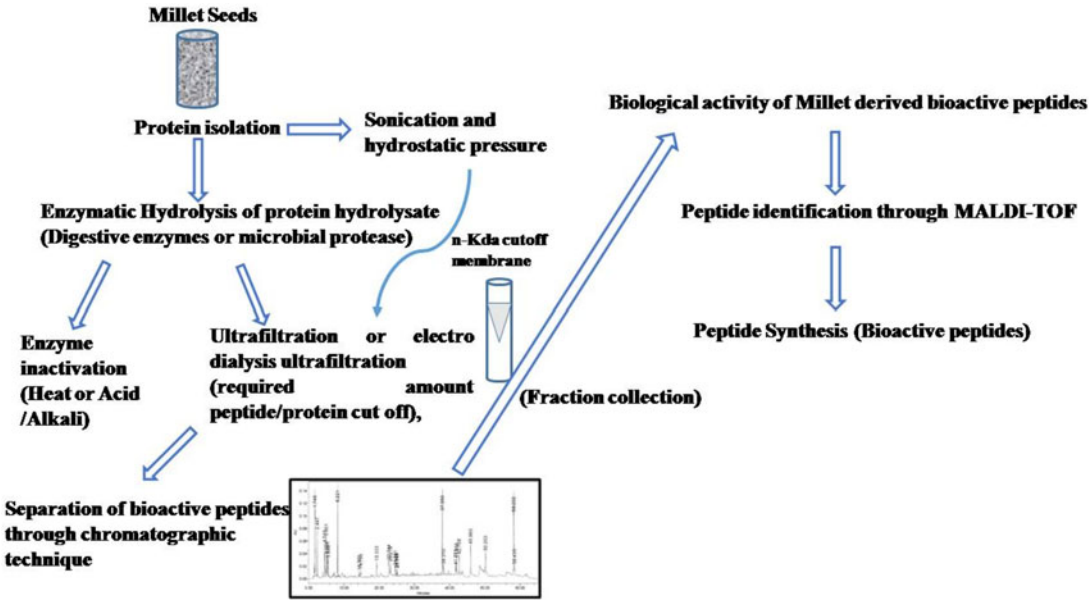

Figure 4. Schematic representation of current techniques applied in the generation of bioactive peptides.

and Matsui 2017; Ganguly, Sharma, and Majumder 2019; Wang, Xie, and Li 2019). Hence, their generation/production is a crucial step and needs utmost attention (Figure 4).

Also, sonication and hydrostatic pressure treatments have also been reported to show the favorable effect on enhanced hydrolysis and release of potent BAPs (Li and Aluko 2010). Once generated, getting these bioactive peptides at high yield and efficacy is bigger bottleneck and hence downstream processing plays an important role. To date, ultrafiltration techniques using varied cutoff membranes of low molecular mass and size-exclusion chromatography have been routinely used to obtain low molecular weight BAMPs. Further, based on the hydrophobic properties of the peptides, reverse-phase HPLC is also used to fractionate peptides (Pownall, Udenigwe, and Aluko 2010).

Further, electro dialysis-ultrafiltration (EDUF), a hybrid method that combines conventional electrodialysis and electrophoresis with an ultrafiltration membrane insert is as an alternative method of peptide separation. This method in addition to separation, also aids in concentration and desalting of the peptides to achieve a high yield (Firdaous et al. 2009; Dlask and Václavíková 2018) and the method was used to fractionate BAPs of low molecular sizes (300 to 700 Da) from flaxseed protein hydrolysate (Poulin, Amiot, and Bazinet 2006, 2007; Doyen et al. 2014). Further, certain adsorbents are used to enrich proteins and peptides based on their amino acid composition. For example, activated carbon is used to obtain peptide fractions rich in branched chain amino acids and low in aromatic amino acids (Adachi et al. 1992; Stone and Kozlov 2014). In addition reports have also demonstrated the used of certain affinity adsorbents for fractionation of proline-rich peptides (Dias et al. 2016).

Most of the millet bioactive peptides discussed in the review have been produced using gastrointestinal enzymes such as trypsin and pepsin as it mimics the normal human digestion. However, pretreatment of the protein before hydrolysis, the degree of hydrolysis, hydrolysis time, and the enzyme–substrate ratios are some of key factors that need to be considered during production of bioactive peptides (Camargo Filho et al. 2008; Xu et al. 2011; Mohamed, Amadou, and Zhou 2012; Amadou et al. 2013; Agrawal, Joshi, and Gupta 2016; Bisht, Thapliyal, and Singh 2016; Agrawal, Joshi, and Gupta 2017; Chen et al. 2017; Guo et al. 2018; Agrawal, Joshi, and Gupta 2019). Other important challenge in the production of BAMPS could be the lesser amount of protein obtained from millets as compared to other food sources such as milk, meat and legumes. However, with an array of functional properties BAMPs possess great promise for commercial applications.

Delivery and bioavailability of bioactive peptides

Use of bioactive peptides including BAMPs in therapeutic application faces a major setback due to lack of effective methods of delivery and bioavailability. The challenge is mainly due to various critical intrinsic physicochemical and biological properties of peptides such as molecular size, charge, lipophilicity, solubility and route of administration (Kumar, Soppimath, and Nachaegari 2006). The major route of administration of peptides so far is limited to parental routes (injections and infusions) and it has its own limitations. Hence, an alternative noninvasive methods are considered to deliver peptides via the oral, transdermal, nasal, pulmonary and buccal administration routes (Wallis et al. 2014). Studies have suggested that the most preferred mode of delivering bioactive peptides is via the oral route because of its ease of administration and reasonably low cost of production. But, even before reaching the site of action to exert their physiological effects, the bioactive peptides faces immense challenges of degradation in the gastrointestinal (GI) tract, permeation through biological membranes, short plasma half-life, instability due to pH and enzymatic digestion (Segura-Campos et al. 2011; Muheem et al. 2016).

Therefore, it is important to generate bioactive peptides that are resistant to GI barriers as well high processing temperatures to accomplish their health promoting properties. Research in this direction has suggested many strategies that include direct structural modification of peptides, use of absorption enhancers and tagging of carrier systems (Kovalainen et al. 2015). These aspects have been extensively reviewed by many authors in recent years (Bruno, Miller, and Lim 2013; Renukuntla et al. 2013; Segura Campos et al. 2013; Muheem et al. 2016). In brief, the direct structural modification is achieved by cyclization, PEGylation, lipidization and hyperglycosylation to enhance stability of bioactive peptides (Yin et al. 2014; Niu et al. 2018). Absorption enhancers are generally co-administered along with peptides to enhance the permeation efficiency of intestinal cell membranes through opening tight junctions, changing the membrane fluidity and changing the mucous viscosity (Aungst 2012). Further, protein transduction domains (PTDs) or cell penetrating peptides (CPPs) have also been reported to enhance delivery of peptides into the cytoplasm via perturbation of the cell membrane or by endocytosis and enhanced intestinal bioavailability (Tünnemann et al. 2006; Buckley, Hubálek, and Rahbek 2016). On the other hand, several carrier systems such as nanoparticles emulsions, microspheres and liposomes are reported to influence the absorption and oral bioavailability of peptides (Malhaire et al. 2016). At present the valid system to study the bioactive peptide delivery and absorption at the intestinal level has been carried out using the Caco-2 model as they mimic mature human enterocytes (Tonolo et al. 2018). Nevertheless, an extensive investigation is still required for the BAMPs to be successfully translated to both therapeutics and nutraceutical applications.

Conclusion

The rising prevalence of lifestyle-associated diseases and concomitant awareness on natural interventions to address these diseases has emphasized the exploration of bioactive peptides apart from natural small molecules. Several bioactive peptides from various dietary sources have demonstrated the compelling evidences as health-improving ingredients against many disease conditions, such as diabetes, obesity, inflammation, cardiovascular disease and cancer through in vitro and animal studies (Korhonen and Pihlanto 2003; Billyard, McTernan, and Kumar 2007; Darewicz et al. 2011; Dang and Sussmuth 2017; Chakrabarti, Guha, and Majumder 2018a). However, there is comparatively less reports on millet-derived bioactive peptides and no comprehensive review yet. Thus, the BMAPs compiled in this review, derived from millet protein hydrolysates possess remarkable biological activities by acting on specific molecular targets of several chronic disorders for the maintenance of health of an individual. Thus, the future research is ought to thrive towards the assessment of their *in-vivo* bioavailability, pharmacokinetics along with their precise molecular mechanism of action, in order to employ BAMPs as health-promoting agents in food systems in the development of new nutraceuticals/functional foods/food supplements.

Acknowledgements

The authors acknowledge all the investigators, researchers and their funding sources that have contributed to an extensive work towards bioactive peptides and human health benefits. We thank Dr. Lakshmikanth Mariyanna and Dr. Gopinath M for the diligent proof reading of the manuscript. The authors also thank the financial assistance provided by the institute CSIR CFTRI and the granting agencies.

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