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Review Article

Angiotensin Converting Enzyme Inhibitory Peptides Derived from Cereals

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Abstract

Hypertension is a major risk factor for cardiovascular disease. Angiotensin I converting enzyme (ACE) elevates blood pressure by generating the vasoconstrictor angiotensin II, in conjunction with the degrading vasodilator, bradykinin. The influences of ACE on blood pressure make it an attractive target for clinical nutritional intervention in hypertension. A number of animal and plant food derived peptides have been reviewed about their *in vitro* and *in vivo* ACE inhibitory activities. However, to date no cereal-derived antihypertensive peptides have been reviewed elsewhere. The aim of this review, thus, is to summarize and discuss the angiotensin converting enzyme (ACE) inhibitory peptides derived from cereals, focusing on the production, purification, mechanism and structural properties as well as their bioavailability.

ABBREVIATIONS

CVD: Cardiovascular diseases; **ACE:** Angiotensin I converting enzyme; **BP:** Blood pressure; **SHR:** Spontaneously hypertensive rats; **UF:** Ultra-filtration; **HPLC:** High pressure liquid chromatography; **RP-HPLC:** Reverse-phase HPLC (RP-HPLC); **IC50:** the half maximal inhibitory concentration; **GI:** Gastrointestinal

INTRODUCTION

Cardiovascular diseases (CVD) are chronic, lifelong diseases caused by interactions among genetic predisposition, health behaviors and the environment, and are currently the leading cause of mortality and disease burden worldwide. Due to lifestyle and dietary factors, Canadians are at high risk of developing CVD, with nine out of ten individuals over the age of 20 having at least one of the major risk factors. A conservative estimate is that 1.6 million Canadians currently have heart disease or are living with the effects of a stroke, and the number of CVD cases is expected to double by 2025. In 2000, CVD was the second most costly contributor to total health costs in Canada ($22.2 billion). Many risk factors for CVD depend considerably on dietary habits, and thus dietary modification is the cornerstone of primary prevention for CVD. By 2025 it is estimated that CVD including coronary heart disease, peripheral artery disease and stroke will become the leading cause of death and disability worldwide [1]. High blood pressure or hypertension is a major, yet controllable, risk factor of CVD. The renin-angiotensin-aldosterone system is considered to play a central role in the maintenance of blood pressure (BP). Angiotensin converting enzyme (ACE) is a multifunctional enzyme present in the rennin-angiotensin system that elevates blood pressure by generating the vasoconstrictor, angiotensin II, in conjunction with degrading the vasodilator bradykinin [2]. Inhibition of ACE activity leads to a decrease in the concentration of angiotensin II, which decreases the tensionin blood vesseles and consequently reduces blood pressure [3]. The influence of ACE on blood pressure has made it an ideal target, and various synthetic medications such as captopril, enalapril, and lisinopril that inhibit angiotensin converting enzyme (ACE) are widely prescribed in the treatment and prevention of cardiovascular disease. However, these drugs are often accompanied by undesirable side effects, including a persistent dry cough that has been reported in up to 44% of patients, as well as less common but more serious side effects such as allergic reactions triggering anaphylaxis, retention of potassium (hyperkalemia) and difficulty swallowing or breathing due to angioedema [4]. In contrast to the synthetic ACE inhibitor drugs, no such side effects have been observed for ACE inhibitors derived from food peptides [5]. In this respect, the search for diet-related preventive agents for hypertension is obviously of interest within the scope of functional foods. Food-derived ACE inhibitory peptides are just the ideal candidates for such products; offering many advantages including safety of the natural product, low cost, and the additional nutritional benefits of the peptides as source of

essential amino acids. These specific peptides are usually inactive within the sequence of the parent protein and can be released in four ways: (a) enzymatic hydrolysis by adding proteolytic enzymes derived from microorganisms or plants, (b) through enzymatic hydrolysis during gastrointestinal digestion and (c) through fermentation or maturation during food processing. However, the most common way to produce bioactive peptides is through enzymatic hydrolysis of whole protein molecules. Most studies for deriving ACE-inhibitory peptides from enzymatic hydrolysis of food proteins have focused on milk proteins [5-7] and fish proteins [8-10] while a few have explored the potential of alternatives such as soybean [11], mushroom [12], garlic [13] and pea [14]. With the growing demand for natural health products that can help to maintain healthy blood pressure, there is a need to consider other possible sources that can tailor to the wide spectrum of consumers with different dietary restrictions. Plant seeds, especially cereals are one of the most important sources of proteins worldwide and cereal proteins have been found to be potential precursors of antihypertensive peptides [15]. In a literature data base survey, twenty-two potential ACE-inhibitory peptides in cereal proteins have been reported [16]. In a recent study, *in silico* digestion of oat and barely by thermolysin resulted in generating 6 and 3 potent peptides from their parent proteins, respectively [17]. Furthermore, a number of cereal food-derived peptides have been shown to have *in vitro* ACE inhibitory activity. These include corn [18-22], wheat [23-26], oat [27-29], rice [30-32], barley [33], buckwheat [34,35] and sorghum [36].

On the other hand, the feasibility of pharmacological application of these peptides depends on their *in vivo* absorption and bioavailability in intact forms in target tissues, thus, in order to use food-derived peptides as enterally potent health-promoting agents, they must show stability against gastrointestinal proteases. In this regard, the spontaneously hypertensive rats (SHR) strain, in which the development of hypertension is very similar to that in human, has extensively been used to test the acute and/or long-term antihypertensive effects of functional food products and bioactive peptides derived from food proteins [37]. Several *in vivo* findings, thus, indicate good possibilities to use cereal proteins as source of blood pressure lowering peptides [33, 37-39].

Here, we review the current literature on the subject of cereal-derived ACE inhibitory peptides including production and purification methods, mechanism and structural-activity relationships, as well as their bioavailability and animal studies.

Angiotensin Converting Enzyme (ACE)

ACE is a metallopeptidase located on the vascular endothelial cells in the brain, lungs, liver, intestine, pancreas, spleen, skeletal muscle, adrenal gland, and placenta [40]. ACE has two roles in blood pressure adjustment: first, it converts angiotensin I to angiotensin II by cleavage of a dipeptide (Histidine-Leucine) from a carboxyl terminal of angiotensin I (decapeptide) thereby producing angiotensin II (octapeptide), a strong vasoconstrictor. For this reason ACE is also called dipeptidyl carboxypeptidase. Angiotensin II is responsible for an increase in blood pressure not only by constricting the blood vessels, but also by releasing the hormone aldosterone from the suprarenal glands, reducing water and sodium excretion from the kidney and causing extra cellular fluid retention [41]. The second role of ACE is to inactivate bradykinin, a potent vasodilator [42]. Because of these two essential roles of angiotensin II, ACE is a main target in the treatment of conditions such as high blood pressure, heart failure, diabetic nephropathy, and Type 2 diabetes mellitus.

The three-dimensional structure of ACE is composed of α-helices containing a zinc ion and two chloride atoms. Zinc is localized in the centre of the molecule, and a deep and narrow channel divides the molecule into two parts. The role of the chloride atom in ACE has been explained as a stimulator in increasing the activity of both ACE domains with more effect on the C-domain active site compared to N-domain [43]. Therefore, it has been demonstrated that both domains have an independent functional active site that possesses a zinc-dependent dipeptidyl carboxypeptidase activity and finally both domains are sensitive to competitive ACE inhibitors [43]. *In vitro* studies show that for complete inhibition of angiotensin I and bradykinin cleavages, inhibitors should block both active sites, however, *in vivo* experiments indicate that the inhibition of one of the domains (either C or N) of ACE by inhibitors is enough for prevention of angiotensin I to II conversion [44].

Methods of Producing Antihypertensive Peptides from Cereals in Comparison to Other Sources

Several parameters affect the bioactive properties of the peptides including the method of production, enzymes applied for hydrolysis, processing conditions, sequence and molecular weight of the resulting peptides, and purification steps.

Biochemical hydrolysis by adding proteolytic enzymes has increasingly become the subject of various researches to produce peptides with specific biological properties from food proteins. The process of using added enzymes instead of chemicals or endogenous enzymes offers many advantages because it provides the possibility of controlling cleavage degree of protein in the substrate and thereby the properties of the resulting products.

The choice of enzyme(s) is usually determined by a combination of efficacy and economics. Several enzyme preparations have been used to produce ACE inhibitors from food proteins; however, the most preferred enzymes by most researchers to generate ACE-inhibitory peptides from cereal proteins are preparations like alcalase, thermolysin, flavourzyme, and gastrointestinal enzymes including pepsin, trypsin and chymotrypsin. The use of commercially available microbial-derived food-grade proteinases to hydrolyze food proteins is advantageous as these enzymes are low-cost, safe and results in high yield of product [7].

Alcalase, an alkaline enzyme produced from *Bacillus licheniformis*, has been proven repeatedly by many researchers to be one of the best enzymes used to prepare cereal-protein hydrolysates [18,23,37] as well as animal protein digestions [7,8,45,46]. Further, alcalase was found to produce the most potent ACE-inhibitory peptides out of five enzyme preparations tested to hydrolyze wheat germ [25]. It has been reported that potent ACE- inhibitory peptides are usually containing hydrophobic amino acid residues at their C-terminal positions, thus, thermolysin, a thermostable neutral metalloproteinase

enzyme produced by the *Bacillus thermoproteolyticus*, has become of interest for producing ACE-inhibitors as it specifically catalyzes the hydrolysis of peptide bonds containing hydrophobic amino acids. The result of some recent studies indicated that thermolysin effectively cleaved cereal proteins especially oat and corn germ into peptides with high ACE-inhibitory activity [17,27,47]. Flavourzyme 1000L (Novo Nordisk, Bagsvaerd, Denmark) also has shown excellent potential for hydrolyzing corn gluten [22].

As an alternative method, gastrointestinal digestion enzymes also have been used in order to examine the effect of these proteases on the production of potent antihypertensive peptides from food proteins. Simulated gastrointestinal (GI) digestion processes have been carried out on various animal protein sources such as milk [48], egg [49], and meat [50]. Cereal proteins are also potential sources for producing such peptides through enzymatic hydrolysis by GI digestion enzymes. As an example, very high potent ACE-inhibitory tri-peptides with the specific amino acid sequence of isoleucine-alanine-cysteine (IAP) have been identified in hydrolysates of wheat gliadin using pepsin preparation [26].

Although the selection of a suitable enzyme is a very important process, there is no standard methodology established yet, however, in some recent studies a modern *in silico* approach have been presented as a useful tool in the evaluation of proteins as a source of ACE inhibitors [17]. In this method, the BIOPEP database has been used to determine whether a specific protein is a potential source of ACE inhibitors and which enzyme preparation must be added to cleave the protein into a specific peptide. The results, based on this model, indicate that, for example, wheat gliadins possessed more potent ACE inhibitors than chicken meat proteins [51]. This approach could be helpful in profiling of potentially active proteins, however, details of the structural properties of active sequences of protein and experimental hydrolysis conditions need to be considered. Using suitable enzyme/ substrate ratios and reaction times permitting the production of hydrolysates with different molecular structures and different biochemical properties [52]. The production of ACE inhibitory peptides using enzymatic hydrolysis has recently been studied using response surface methodology and it was shown that the ACE inhibitory activity of oat [27], wheat [53] and rice [30] protein hydrolysates could be controlled by systematically regulating process conditions.

Recent developments have taken place in the production of ACE inhibitory peptides and also other bioactive peptides which include digestion in membrane reactors. In enzymatic membrane reactors, hydrolysis of food proteins is combined with purification of the bioactive peptides from the reaction mixture through the use of filtration or selective precipitation. Antihypertensive peptides produced from corn hydrolysates using this technology significantly lowered the blood pressure of spontaneously hypertensive rats [54].

In order to improve the quality of enzymatic hydrolysis or produce peptides with higher activity, some other techniques, such as high pressure, heat denaturation, and ultrasonic power were also investigated. The latter technique, especially, has been reported in cereal hydrolysis since it could break down the complex protein matrix of such sources effectively. For instance, ultrasonic pretreatment of oat-seed protein solution has made a significant impact on ACE inhibitory activity [28]. The researchers verified that the increase in protein hydrophobicity caused by ultrasound is one of main reasons for a significant improvement of hydrolysates ACE inhibitory activity. This technique also could significantly enhance enzymatic hydrolysis in preparing ACE-inhibitory peptides from other cereals such as wheat [24] and corn [55]. Ultra-filtration (UF) is technique that is becoming a well-known method in concentration and fractionation of ACE inhibitory peptides of defined molecular weight ranges, especially for obtaining fractions containing low molecular weight peptides. Application of UF to enrich antihypertensive peptides from cereals [54,56] as well as animal protein sources [8,57,58] has been reported in the literature. Further purification steps are often utilized to obtain pure peptides. Gel filtration chromatography followed by reverse-phase HPLC (RP-HPLC) has been used to fractionate and purify ACE-inhibitory peptides from cereals in several studies. First, gel filtration chromatography was used to obtain fractions containing low molecular weight peptides and these peptides were then further fractionated on a RP-HPLC based on their hydrophobic properties. The resulting fractions with high ACE-inhibitory activity capable of withstanding further *in vivo* proteolytic digestion were applied on a peptide sequencer to identify their structure. Based on these three steps purification, potent peptides have been isolated from wheat [26], rice [27], oat [27], corn [18] and buckwheat [56]. In addition, immobilized metal-affinity chromatography followed by RP-HPLC has been reported as a successful method for isolation of peptides from wheat [17]. Structural properties of these purified peptides influence their activity; hence, the choice of purification method(s) requires an understanding of the structural requirements of the target peptides.

Mechanisms and Structural Properties of Angiotensin Converting Enzyme Inhibitory Peptides Derived from Cereal and Other Sources

The inhibition of the activity of ACE or its blockage lowers the level of angiotensin II, greatly aiding in diminishing the hypertensive effects, and therefore leading to the treatment of hypertension [59]. The concept of blocking ACE forms the central idea of the research that has been carried out in this area over the past few decades. Clearly, the focus of the research has been on finding a potential ACE inhibitor either by natural or artificial means.

The first significant breakthrough in this direction took place in the 1960's with the discovery of an ACE inhibitor that was extracted from the venom of a Brazilian snake, *Bothrops jararaca* [60]. The crude mixture of peptides was extracted and first described as a bradykinin-potentiating factor. Amino acid sequences of this factor were determined and named bradykinin potentiating peptides [60]. However, due to the fact that these peptides were present in low quantities in the snake venom, the focus of the research shifted to finding alternative sources of ACE inhibitors. Subsequent research revealed that these peptides could be obtained from different food sources.

Although the relationships between the structural properties

and functional activities of peptidic ACE inhibitors have not been fully understood, some common structural properties of ACE-inhibitory peptides are worth noting [61]. Tables 1 and 2 are presenting the source, preparation method, sequence and IC_{50} of most potent food-derived ACE-inhibitory peptides which have been identified to date. These peptides are generally short sequences with only two to nine amino acids notably the di or tri-peptides because of their high competitive affinity with the ACE active site. This is in agreement with the results of Natesh and co-workers [62] who demonstrated from crystallography studies that the active site of ACE cannot accommodate large peptide molecules. The inhibitory activity towards enzymes can be expressed as an IC_{50} value; referring to the concentration of inhibitor needed to inactivate 50% of the enzyme activity under the experimental conditions. Structure–activity relationships of synthetically produced analogues of ACE inhibitory peptides have also indicated that competitive binding to ACE is strongly influenced by the C-terminal tri-peptide sequence. At these positions, the presence of hydrophobic aromatic amino acids, such as tyrosine, phenylalanine, tryptophan, or amino acids with hydrophobic branched side chains, such as valine, leucine and isoleucine, generally leads to increased ACE inhibitory activity. Many ACE inhibitory peptides also contain a proline residue at their C-terminal position [63,64]. Furthermore, several ACE inhibitory peptides have an arginine or lysine residue at their C-terminal end, suggesting that the positive charge on the e-amino group contributes to their inhibitory activity [64]. The active forms of numerous ACE-inhibitory peptides derived from cereal are di- or tri-peptides (Table 1). ACE inhibition studies with di-peptides of cereal showed that C-terminal phenylalanine, tryptophan, arginine and tyrosine are the most effective in enhancing substrate binding. The di-peptides alanine-phenylalanine (AF) and threonine-phenylalanine (TF) from wheat [25], valine-tryptophan (VW) and tyrosine-tryptophan (YW) from rice sake [31], alanine-tyrosine (AY) from corn [18] and valine-tyrosine (VY) from rice hydrolysates [37] are examples of such peptides.

Furthermore, in cereal-derived ACE inhibitory peptides, proline and tyrosine seem to be the most effective residues to increase the ACE inhibiton. Of the twenty three isolated tri-peptides with IC_{50} less than 20 μM from different grains, twenty of them contain proline or tyrosine at their C-terminal position (Table 1). As examples, strong potent ACE-inhibitory peptides with the sequence of leucine-proline-proline (LPP), leucine-agrinine-proline (LRP), leucine-serine-proline (LSP) and leucine-glutamine-proline (LEP) were obtained from corn endosperm [20]. The strong ACE inhibitory activities of tyrosine-glutamine-tyrosine (YEY) and proline-serine-tyrosin (PSY) isolated from buckwheat hydrolysates [35] by GI digestion enzymes also supported the importance of tyrosine at the carboxyl terminal.

Peptide conformation, that is the structure adopted in the specific environment of the binding site will influence binding to ACE for long chain peptides [65,66]. Isolated penta-peptides from wheat (Table 1) showed high ACE- inhibitory activity *in vitro*. However, by considering poor resistance of longer peptides to digestion by gastrointestinal proteases and low susceptibility to absorption [25], the isolated peptides with more than four amino acids might be of little significance toward the *in vivo* antihypertensive effect regardless of their high *in vitro* activity.

Apart from C-terminal, central domains are shown to affect binding to ACE enzyme for some identified peptides. Recently, Thewissen *et al* (2011) fractionated peptides from wheat gliadin to either the central domains or terminal domains to relate ACE inhibitory properties to structural properties of peptides. These fractions were screened for ACE inhibitory activity. Central domains and terminal domains of gliadins were different in their levels of proline and other hydrophobic amino acids, such as isoleucine, leucine, valine, which contributed to ACE-inhibitory activity. Therefore, enrichment of peptides containing those amino acids may lead to peptide fractions with increased ACE-inhibitory potential. Based on this information, additional peptidases were then selected using *in silico* technique to increase ACE inhibitory activity [23]. Hence, structure-activity relationship prediction before enzymatic process leads to production of peptides with high ACE inhibitory activity. In another study, using wheat germ as the starting material, the effect of incubation conditions were adjusted, and as a result five new antihypertensive peptides were identified. Interestingly, three of them had valine at their C-terminal and the most potent peptide had the sequence alanine-methionine-tyrosine (AMY).

The peptides identified from animal or other plant sources are also following these structure-activity relationships (Table 2). Of the eight ACE-inhibitory peptides isolated from dried bonito by Fujita and Yoshikawa [67], the tri-peptides leucine-lysine-proline (LKP) containing proline at the C-terminal showed the highest hypotensive activity both *in vitro* and *in vivo.* Similarly, the peptide LKP has been isolated from thermolysin digestion of chicken muscle, and , both isolates were shown to have an IC_{50} of 0.32 μM *in vitro*. Specific ACE inhibitor peptides, derived from sardine and tuna muscles [68,69] were shown to have amino acids sequences of KW, AKK, GWAP and IF, VWIG, PTHIKWGD.

Digestion of other plant sources, besides cereals, could also enhance production of antihypertensive peptides. The two potent peptides aspartate-leucine-proline (DLP) and aspartate-glycine (DG) were isolated from alcalase hydrolysate of soy [70]. *In silico* analysis of pea, on the other hand, resulted in identification of potent peptides of leucine-tyrosine (LY), leucine-lysine-proline (LKP) and leucine-glysine-proline (LGP) [71]. These findings were in line with earlier results [63] also showed that the hydrophobicity of the carboxyl terminal amino acid was the most important factor affecting the overall binding of the peptides to the active site of ACE. Similarly, the most well-known tri-peptides from food proteins, isoleucine-proline-proline (IPP) and valine-proline-proline (VPP), are also containing proline in their middle position and C-terminal domain. These two peptides formed from milk caseins [72] by certain lactobacillus helveticus strains, have already been commercialized as Calpis and Evouls prodrug products for hypertensive patients in Japan and Finland.

Currently, food-based ACE-inhibitory peptides are not available in the North American market in either nutraceutical or functional food format. However, further validation of the *in vivo* hypertensive activity of food-derived ACE inhibitory peptides will present possibilities for their use in the future to prevent and treat hypertension.

Table 1: Potent ACE Inhibitory Peptide Sequences Derived from Cereal Sources.

Source	Peptide Sequence	Preparation's Method	IC_{50} μM	References
Rice Sake	VW	Fermentation	1.4	[31]
Wheat & Oat	IW	*In silico* technique	2.0	[16]
Oat, Rye & Wheat	IY	*In silico* technique	2.1-3.7	[16]
Oat, Rye & Wheat	FY	*In silico* technique	3.7	[16]
Oat, Rye & Wheat	PR	*In silico* technique	4.1	[16]
Oat & Wheat	VY	*In silico* technique	7.1	[16]
Oat & Wheat	VF	*In silico* technique	9.2	[16]
Rice Sake	YW	Fermentation	9.4	[31]
Buckwheat	VK	Pepsin+Chymotrypsin+ Trypsin	13.0	[35]
Corn	AY	Alcalase	14.2	[18]
Wheat	AF	alkaline protease	15.2	[25]
Wheat	TF	alkaline protease	17.8	[25]
Rice	VY	Alcalase	18.2	[37]
Wheat Germ	QV	Water Extraction	26.82	[53]
Buckwheat	YQ	Pepsin+Chymotrypsin+ Trypsin	628.0	[35]
Wheat Bran	IY	autolysis	nd	[73]
Wheat Bran	VY	autolysis	nd	[73]
Corn endosperm	LRP	Thermolysin	0.27	[20]
Oat	LKP	*In silico* technique	0.32	[16]
Wheat Germ	IVY	Alcalase	0.48	[39]
Wheat	GGY	*In silico* technique	1.3	[16]
Oat & Corn	LSP	*In silico* technique	1.7	[16]
Corn endosperm	LSP	Thermolysin	1.7	[20]
Corn endosperm	LEP	Thermolysin	1.9	[20]
Oat, Rye &Wheat	LQP	*In silico* technique	2.0	[16]
Wheat	VRP	*In silico* technique	2.2	[16]
Rye & Oat	PRY	*In silico* technique	2.5	[16]
Wheat	IAP	Pepsin	2.7	[26]
Buckwheat	YQY	Pepsin+Chymotrypsin+ Trypsin	4.0	[35]
Oat & Wheat	GPV	*In silico* technique	4.7	[16]
Wheat	DLP	*In silico* technique	4.8	[16]
Wheat	IPP	*In silico* technique	5.0	[16]
Wheat Germ	AMY	Water Extraction	5.86	[53]
Buckwheat	GPP	Participation	6.25	[56]
Oat & Wheat	IRA	*In silico* technique	6.4	[16]
	VPP	*In silico* technique	9.0	[16]
Wheat & Corn	LPP	*In silico* technique	9.6	[16]
Oat & Wheat	VSP	*In silico* technique	10.0	[16]
Rice Sake	VWY	Fermentation	10.5	[31]
Corn	GPP	Flavourzyme	17.6	[22]
Buckwheat	LGI	Pepsin+Chymotrypsin+ Trypsin	29.0	[35]
Corn	LPF	Flavourzyme	40.0	[22]
Buckwheat	ITF	Pepsin+Chymotrypsin+ Trypsin	49.0	[35]
Oat	GYR	Trypsin	77.3	[74]
Wheat Germ	VEV	Water Extraction	115.20	[53]
Wheat	VFPS	Alcalase	0.46	[25]

Wheat	TVPY	Alkaline protease	2.0	[25]
Rice sake	v	Fermentation	3.4	[31]
Wheat	TAPY	Alkaline protease	13.6	[25]
Corn	SQPP	Flavourzyme	17.2	[22]
Corn	PNPY	Flavourzyme	30.7	[22]
Buckwheat	INSQ	Pepsin+Chymotrypsin+ Trypsin	36.0	[35]
Corn Gluten	PSGE	Pascalase	100	[75]
Wheat	DYVPG	Alkaline protease	0.72	[25]
Wheat	TVVPG	Alkaline protease	2.2	[25]
Wheat	DIGYY	Alkaline protease	3.4	[25]
Rice Sake	IYPRY	Fermentation	4.1	[31]
Wheat Germ	NPPSV	Water Extraction	40.56	[53]
Wheat	GGVIPN	Alkaline protease	0.74	[25]
Corn	SPPPFYL	Flavourzyme	63.0	[22]
Wheat	APGAGVY	Alkaline protease	1.7	[25]

nd, not determined.

Table 2: Potent ACE Inhibitory Peptide Sequences Derived from Other Sources.

Source	Peptide Sequence	Preparation's Method	IC_{50} μM	References
Milk (α-casein)	TVY	Trypsin	15	[76]
Milk (β-casein)	VPP	Fermentation	9.0	[72]
Milk (β-casein)	IPP	Fermentation	5.0	[72]
Cheese (whey)	IPA	Proteinase K	141.00	[77]
Milk (α-casein)	FFVAP	Trypsin	6.0	[76]
Milk (β-casein)	KVLPVP	Fermentation	5.00	[78]
Milk (α-casein)	YKVPQL	Alcaline Proteases	22	[79]
Milk (whey)	WLAHK	Trypsin	77.00	[80]
Milk (whey)	ALPMHIR	Trypsin	42.6	[81]
Soy Protein	DG	Alcalase	12.3	[70]
Soy Protein	DLP	Alcalase	4.8	[70]
Soy Protein	HHL	Fermentation	4.9	[82]
Chicken Muscle	LKP	Thermolysin	0.32	[2]
Dried Bonito	LKP	Thermolysin	0.32	[2]
Sardine	KW	Alcaline Proteases	1.63	[68]
Sardine	AKK	Alcaline Proteases	3.13	[68]
Sardine	GWAP	Alcaline Proteases	3.86	[68]
Tuna Muscle	PTHIKWGD	nd	1.5	[69]
Tuna Muscle	IF	nd	70	[69]
Tuna Muscle	VWIG	nd	110	[69]
Pea	LKP	*In silico* technique	0.32	[71]
Pea	LGP	*In silico* technique	0.72	[71]
Pea	IY	*In silico* technique	2.1	[71]

Bioavailability and Animal Study of Cereal-Based Antihypertensive Peptides

The physiological effects of bioactive peptides depend on the ability to reach their target organs in an active form. This implies resistance to gastrointestinal enzymes and brush border membrane peptidases, and absorption through the intestinal epithelium.

Usually, the first step to investigate the hypotensive potential of ACE inhibitory peptides *in vivo* is *via* animal studies using spontaneously hypertensive rats. Numerous rat studies have been performed to determine the hypotensive effects of food protein derived ACE inhibitors. The BP responses in SHRs following oral ingestion or intravenous administration of ACE

Table 3: Summary of Hypotensive Effects of ACE-Inhibitory Peptides Derived from Cereals in Spontaneously Hypertensive Rats.

Source	Peptide Sequence	Dose	Activity	References
Corn digested by alcalase	AY	50 mg/kg	Decrease SBP 9.5 mmHg at 2h	[18]
Corn digested by pescalase	PSGE	30 mg/kg	Decrease SBP 5.5 mmHg at 15 min	[75]
Corn digested by thermolysin	LSP	5000 mg/kg	Decrease SBP 14.5 mmHg at 6h	[20]
Rice digested by alcalase	VY	30 mg/kg	Decrease SBP 25.6 mmHg at 6h	[37]
Rice sake	VW, YW, VWY,YGGY, IYPRY	100 mg/kg	Decrease SBP between 13 mmHg to 18 mmHg at 30h	[31]
Wheat digested by pepsin	IAP	150 mg/kg	Decrease SBP 9.5 mmHg at 3h	[26]
Buckwheat digested by GI enzymes	AMY	100 mg/kg	Decrease SBP 9.3 mmHg at 2h	[35]
Wheat digested by Alcalase + α-amylase	IVY	50 mg/kg	Decrease SBP 10.3 mmHg at 3h	[39]

inhibitory food protein hydrolysates and derived peptides from bovine milk, animal, fish, plant and miscellaneous protein has been reviewed elsewhere [66].

Hypotensive effects of ACE-inhibitory peptides derived from cereals in spontaneously hypertensive rats have been summarized in Table 3. In general, systolic blood pressure responses range from – 5.5 to – 25.6 mm Hg. The wide variation in blood pressure responses may be due to variations in sample type, the dosage and administration, the mode of delivery and the method for the measurement of blood pressure. For example, injection of a total of 150 mg/kg of isoleucine-alanine-proline (IAP) derived from wheat gliadin can result in a significantly larger decrease in systolic blood pressure of spontaneously hypertensive rats than injection of a total of 50 mg/kg of same peptides [26]. Oral administration, in some cases can release the active form of certain peptides during gastrointestinal processes. An example is that of the peptide isoleucine-valine-tyrosine (IVY) which was found to be hydrolyzed to the shorter di-peptides valine-tyrosin(VY) by cellular peptidase prior to transport across the intestinal epithelium. This shorter form has been detected in human and rats plasma after oral administration [39]. Three new potent peptides, FW (IC_{50}=3.9 μM), LQQGG (IC_{50}=8.6 μM) and ATF (IC_{50}=9.6 μM) from barley protein were further released by GI enzymes after *in silico* digestion of thermolysin. These findings indicate that animal studies may be used as a tool to verify the action of specific ACE inhibitory peptides in complex mixtures of hydrolysates. However, further investigation into the clinical antihypertensive effect of ACE inhibitory peptides derived from cereals is necessary.

CONCLUSIONS

Hypertension, which is estimated to affect one third of the western population, is a major risk factor for cardiovascular disease such as stroke and coronary heart disease. There are a great number of pharmaceuticals that have been proved to be effective in lowering blood pressure. Diet and lifestyle modification may also represent effective tools for the prevention of hypertension, which could decrease the requirement for antihypertensive drugs that usually have side effects during treatment of the disease. In this regard, food researchers have extensively studied peptides derived from food proteins as potential alternatives to prevent and/or treat hypertension. Angiotensin converting enzyme (ACE) is one of the main regulators of blood pressure through two physiological mechanisms. It elevates blood pressure by generating the vasoconstrictor angiotensin II, in conjunction with degrading the vasodilator bradykinin. By inhibiting this enzyme food derived peptides have been shown to lower blood pressure in animal and clinical studies. The current literature has shown that peptides derived from cereal proteins possess high ACE inhibitory activity *in vitro* and *in vivo*.

Despite the fact that *in vitro* and *in vivo* findings of ACE inhibitory peptides derived from cereals are good starting points, future research efforts should be directed toward evaluation of bioavailability of such peptides in human subjects, better understanding of structure-activity relationships of the potent peptides and overall possible use as health-promoting agents in food systems.

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