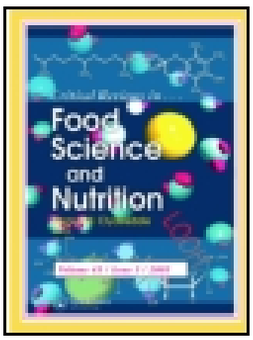

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Bioactive peptides from selected latin american food crops – A nutraceutical and molecular approach

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ABSTRACT

This review reported an updated survey on the molecular functional properties of bioactive peptides derived from different Latin American ancient grains such as Maize, common Bean, Amaranth, Quinoa and Chia seeds. Seed storage proteins ecrypt in their sequences diverse peptides associated with a wide range of beneficial effects on the human health and the most studied are antihypertensive, anti-cholesterolemic, antioxidant, anti-inflammatory, anticancer, antimicrobial and immunomodulatory properties. Additionally, in the last decades molecular properties have been also used for their characterization to understand their activities and it makes them highly attractive to be incorporated into food formulations and to complement or replace some conventional cereal grains. Due to the nutraceutical effects, today, these seeds are one of the main gastronomic trends of consumption worldwide due to their nutritional benefits and are part of the shopping lists of many people, among them vegetarians, vegans, celiacs or lovers of raw food. These seeds are a legacy of pre-Columbian civilizations reason why in our time they are considered as "Superfoods of the Gods", "The pre-hispanic superfoods of the future" and "The new golden seeds of the XXI century".

KEYWORDS

Nutraceutic peptides; Maize; Amaranth; Quinoa; Common bean; Chia

1. Introduction

Nowadays, different scientific areas like chemistry, biology, medicine and pharmacology have focused their research on foods and food products, manly due to their health benefits. Bioactive substances are known as "components of foods that modulate metabolic processes, provide benefits to health and a positive impact on the function of the body". The role of a healthy diet for the prevention of diseases is well accepted today, and the border between food and medicine is very small (Pravst 2012; Minkiewicz et al. 2015).

Proteins are important components of foods, and are essential for the maintenance of the body; they are also a source of bioactive peptides which exert biological functions to promote health and prevent some diseases. Specific amino acids sequences encrypted in the protein have health effects, but it is still unclear if they are more potent than the whole proteins. These short amino acid sequences are found in a wide range of proteins and varied foods. They can play an important role as a fragment of the whole protein (epitopes responsible for interactions between proteins and antibodies) or they may be useful after the release by proteolytic enzymes. Peptides with two or three amino acids are very useful because they pass easily through the gastrointestinal tract to the blood. It is possible that each protein is a source of biological active dipeptides and tripeptides, and thus it is possible that all existing proteins are precursors of peptides with certain biological activity. The study of the proteome, or total set of proteins in a food in particular, may be of great importance upon providing adequate food for the mankind (Minkiewicz et al. 2008; Möller et al. 2008; Minkiewicz et al. 2015; Wang et al. 2015; Cicero, Fogacci, and Colletti 2017).

Bioactive peptides have been known for several years and their identification in plant and animal sources are increasing as result of new scientific methods. These compounds have high nutraceutical potential with great benefits for human health; i.e, on blood pressure and lipid metabolism; as well as anticancer, immunomodulatory, analgesic, antimicrobial, antioxidants, anti-thrombosis, anti-atherosclerotic, opioid and anti-inflammatory; some of them have more than one activity. They are also useful to improve the absorption of minerals (Hartmann and Meisel 2007; Cicero et al. 2011a; Udenigwe and Aluko 2012; Aluko 2015; Cicero and Colletti 2015; Maestri, Marmiroli, and Marmiroli 2016; Bouglé and Bouhallab 2017).

Bioactive peptides are product of the hydrolysis by gastrointestinal digestive enzymes (pepsin, trypsin, and chymotrypsin), or by *in vitro* producers with enzymes, temperature or pH. They usually are composed by two and up to 30 amino acids, with some exceptions, such as Lunasin (peptide derived from cereals and soy proteins) that has 43 amino acids. Other characteristics of the bioactive peptides are the presence of hydrophobic amino acids in their sequences, a positive charge and the resistance to digestion by proteases and peptidases, and a proline C terminal. Small peptides with a dipeptide of proline-proline at their C terminal are the most resistant to degradation by proteases and peptidases of stomach, pancreas or intestine.

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Large peptides (with 6 or more) are usually active outside the intestinal epithelium (Galvez et al. 2001; Korhonen and Pihlanto 2003; Panchaud, Affolter, and Kussmann 2012; Perez Espitia et al. 2012; Maestri, Marmiroli, and Marmiroli 2016).

By silico, *in vitro, ex vivo* and *in vivo* models have been reported over 3566 different potential bioactive peptides and distinct biological activities; this information has been compiled into a peptide database (BIOPEP database) (Minkiewicz et al. 2008). Bioactive peptides are identified by mass spectrometry, and used for comparative proteomics. At present, there are several databases to analyze food peptides (Table 1) (Dave et al. 2016; Maestri, Marmiroli, and Marmiroli 2016). On the other hand, Gupta et al. (2013) built a Web site to predict the toxicity of peptides called ToxinPred. This site has been very useful for scientists because it allows to determine the appropiate function of the peptide in human health.

2. Functional properties of bioactive peptides

Bioactive peptides have a wide range of benefits for the human body, mainly due to the composition of amino acids present in each peptide and the different reactivity; the most studied are antihypertensive, anti-cholesterolemic, antioxidant, anti-inflammatory, anticancer, antimicrobial and immunomodulatory properties. Beside, some peptides have multimodal activities and can exert more than one beneficial effect (Meisel 2004; Hartmann and Meisel 2007; Santiago-López et al. 2016).

Table 1. Bioactive peptides database.

Name of Database	Description of database	Link
ACEpepDB	Peptides inhibiting Angiotensin I converting enzyme	http://www.re3data.org/repository/r3d100010972
AHTPDB	Antihypertensive peptides	http://crdd.osdd.net/raghava/ahtpdb/
AllergenOnline Celiac Disease	Database of celiac-toxic peptides and proteins	http://www.allergenonline.org/celiachome.shtml
AMPer	Antimicrobial peptidess	https://omictools.com/amper-tool
ANTISTAPHYBASE	Antimicrobial peptidess	http://www.antistaphybase.com
ArachnoServer	Toxic peptides and proteins from spider venoms	http://www.arachnoserver.org/mainMenu.html
ATDB	Animal Toxin Database	http://bactpepdb.rpbs.univ-paris-diderot.fr/cgi-bin/links.pl
APD	Antimicrobial and anticancer peptides	http://aps.unmc.edu/AP/main.php
AVPdb	Antiviral peptides	http://crdd.osdd.net/servers/avpdb/
BactPepDB	Predicted bacterial peptides	http://bactpepdb.rpbs.univ-paris-diderot.fr/cgi-bin/home.pl
BACTIBASE	Antibacterial peptides	http://bactibase.hammamilab.org/main.php
BAGEL2	Antibacterial peptides	http://bagel2.molgenrug.nl
BAGEL3	Database of antibacterial peptides (bacteriocins)	http://bagel.molgenrug.nl
BaAMPs	Antimicrobial peptidess against microbial biofilms	http://www.baamps.it
Brainpeps	Blood-Brain peptides	http://brainpeps.ugent.be
BIOPEP	Biologically active peptides	http://www.uwm.edu.pl/biochemia/index.php/pl/biopep
CAMP	Antimicrobial peptides and proteins	http://www.camp.bicnirrh.res.in
CPPSite	Cellular peptides	http://crdd.osdd.net/raghava/cppsite/
CancerPP	Anticancer peptides	http://crdd.osdd.net/raghava/cancerppd/
Cybase	Cyclic proteins and peptides with various bioactivities	http://www.cybase.org.au
DADP	Anuran defense peptides	http://split4.pmfst.hr/dadp/
DAMPD	Antimicrobial peptides.	http://apps.sanbi.ac.za/dampd/
Defensins knowledgebase	Database of defensine from antimicrobial peptides	http://defensins.bii.a-star.edu.sg
Effective DB	Database of predicted secreted bacterial peptides	http://effectors.org
EROP-Moscow	Regulatory oligopeptides	http://erop.inbi.ras.ru
HIPdb	HIV inhibiting peptides	http://crdd.osdd.net/servers/hipdb/
MHCBN	Major Histocompatibility Complex (MHC) Binding,Non-binding peptides and T-cell epitopes	http://crdd.osdd.net/raghava//mhcbn/
HMRBase	Hormones and peptides	http://crdd.osdd.net/raghava/hmrbase/
NeuroPep	Neuropeptides	http://isyslab.info/NeuroPep/
Norine	Nonribosomally synthesized bioactive peptides.	http://bioinfo.lifl.fr/norine/
ParaPep	Antiparasitic peptides	http://crdd.osdd.net/raghava/parapep/
PepBank	Peptides shorter than 20 residues	http://pepbank.mgh.harvard.edu
PepBind	Protein-peptide interactions	https://test5.bicpu.edu.in
Peptaibols	Antimicrobial peptides	http://peptaibol.cryst.bbk.ac.uk/home.shtml
PeptideAtlas	Compendium of peptides from multi-organisms	http://www.peptideatlas.org
PeptideDB	Compendium of peptides from multi-organisms	http://www.peptides.be
PeptideLocator	Identified bioactive peptides within protein sequences	http://bioware.ucd.ie/~compass/biowareweb/Server_pages/biopred.php
PhytAMP	Antimicrobial Plant peptides	http://phytamp.hammamilab.org/main.php
Quorumpeps	Resource of quorum sensing signalling peptides	http://quorumpeps.ugent.be
SMS	A database to study the structural plasticity of short peptide fragments in non-redundant proteins.	http://cluster.physics.iisc.ernet.in/sms/
SPdb	A signal peptide database containing signal sequences of archae, prokaryotes and eukaryotes	http://proline.bic.nus.edu.sg/spdb/
SwePep	A database of biologically active peptides including sophisticated computing tools for peptide mass spectra interpretation.	http://www.swepep.org
YADAMP	Database of Antimicrobial Peptides	http://yadamp.unisa.it
THPdb	Therapeutic peptides	http://crdd.osdd.net/raghava/thpdb/
ToxinPrep TumorHoPe	*In silico* method to predict and design toxic/non-toxic peptides Tumor-recognizing peptides	http://crdd.osdd.net/raghava//toxinpred/ http://crdd.osdd.net/raghava/tumorhope/

2.1. Anti-hypertensive

Hypertension is the major risk factor for the myocardial infarction, heart failure, atherosclerosis and kidney disease. The use of nutraceuticals in the treatment or prevention of this condition is of great impact to reduce the side effects of the antihypertensive drugs (Sirtori, Arnoldi, and Cicero 2015; Borghi and Cicero 2017).

The main mechanism to regulate blood pressure is the renin-angiotensin aldosterone system (ACE), which plays an important role in the control and regulation of blood pressure and salt balance. Antihypertensive drugs, like Captopril, Lisinopril and Enalapril, inhibit the renin-angiotensin system but produce some side effects (sleep apnea, dry cough, angioedema, etc). Some bioactive peptides show competitive and/or non-competitive ACE inhibition, which is responsible of the conversion of angiotensin I in angiotensin II. Angiotensin-I catalyzes the conversion to the vasoconstrictor angiotensin II, which increases the peripheral vascular resistance, inducing hypertensive action. ACE also determines the cleavage and inactivation of bradykinin, a vasodilator peptide. The increased of protein intake has been associated with a reduced risk of increased blood pressure and coronary heart diseases; food-derived peptides have been identified as potential antihypertensive agents. Peptides with ACE inhibitory activity are small and have hydrophobic amino acids (W, Y, F, and P) (Table 2) in C-terminal which determine the affinity to the active site of the enzyme. In addition, the effectiveness of these peptides depends on their resistance to degradation, to the absorption into the blood stream and to amino acid sequence. Many peptides have been identified with this activity in protein of plants, animals and microorganisms, and the beneficial effect on blood pressure and vascular system has been confirmed in animal and human models (Foltz et al. 2007; Aluko 2015; Mora and Hayes 2015; Cicero et al. 2016; Bhat, Kumar, and Bhat 2017; Bouglé and Bouhallab 2017).

The richest source of protein and bioactive peptides is milk, which have been identified as antihypertensive agents; IPP and VPP are the best-characterized in human studies (Table 2). Cicero et al. (2011b) reported that in Asian patients the most efficient dose of peptides to decrease blood pressure ranged between 3.07 mg/d (1.60 mg of VPP and 1.47 mg of IPP) and 52.5 mg/d (30 mg of VPP and 22.5 mg of IPP), and was independent of age, by addition, the systolic and diastolic pressure decreased around 5 and 2 mm Hg, respectively, without negative impact on health; however, the European Food Safety Authorities (EFSA) rejected this health benefit (Jauhiainen et al. 2005; Sano et al. 2005; Panel 2012; Bhat, Kumar, and Bhat 2017). This kind of antihypertensive peptides can be found now on the market. Serum proteins and casein are bioactive peptides with significant antihypertensive effects in normaltense/pre-retinopathy obese subjects. Numerous studies in humans and animals show that milk, whey and casein peptides are able to inhibit ACE and may positively affect blood pressure. Peptides sequences from some animals proteins are shown in Table 2 (Bhat, Kumar, and Bhat 2015; Nongonierma and FitzGerald 2015).

The search for ACE inhibitory peptides has been increasing in the last years; Nakashima et al. (2002) identified two in porcine skeletal muscle, MNPPK and IWWNP, and Katayama et al. (2003) found RMLGQTPT. In porcine myosin, Katayama et al. (2003; 2007) identified VKKVLGNP, KRVITY and KRQKIDI, and Arihara et al. (2001) described ITTNP and NNPPK. Jang and Lee (2005) identified VLAQYK in beef. Kawasaki et al. (2000) observed a reduction of blood pressure in patients with a daily ingestion of 3 mg of sardine dipeptide VY, 9 and 5 mm Hg in systolic and diastolic pressure, respectively.

Table 2. Bioactive peptides from various animal proteins with antihypertensive/ACE-inhibition activity.

Protein source	Peptide/sequence
Casein	FP
	YP
	IPP
	IPA
	GKP
	LKP
	VPP
	FFVAP
	LKPNM
	VYPFPG
	YKVPQL
	EMPFPK
	TTMPLW
	FALPQY
	YQEPVL
	KKYKVPQ
	AVPYPQR
	FALPQYLK
	YPVEPFTE
	RPKHPIKHQ
	GPVRGPFPIIV
	FFVAPFPEVFGK
Whey proteins	YP
	LLF
	IPA
	WLAHK
	ALPMHIRY
Porcine skeletal muscle Myosin	IWWNP
	TNP
	ITTNP
	MNPPK
	KRVITY
	KRQKYDI
	RMLGQTPT
	VKKVLGNP
Gelatin (bovine skin)	GPL
	GPV
Chicken	IKW
	LKP
	GFHyGTHyGLHyGF
Egg	LW
	YPI
	SALAM
	RADHP
	RADHPF
	RADHPFL
	ERKIKVYL
	FRADHPFL
	RADHPFLT
	FFGRCVSP
	YAEERYPIL
Fish	VY
Beef	VLAQYK
	LAQYWK

The amino acid nomenclature: A: Alanine; C: Cysteine; D: Aspartic acid; E: Glutamic acid; F: Phenylalanine; G: Glycine; H: Histidine; I: Isoleucine; K: Lysine; L: Leucine; M: Methionine; N: Asparagine; P: Proline; Q: Glutamine; R: Arginine; S: Serine; T, Threonine; V: Valine; W: tryptophan; Y: Tyrosine; B: either of D or N; Z: either of E or Q.

Saiga et al. (2003) reported the strongest ACE inhibitory activity with GFHYGTHYGLHYGF in chicken breast meat, and Cheng et al. (2008) (Cheng et al. 2008) in chicken leg bones. Also, it has been reported that ovokinin, an octapeptide (FRAHPFL) isolated from ovalbumin, significantly lowered systolic blood pressure in spontaneously hypertensive rats. Some analogs of this peptide also exhibited antihypertensive properties; with the replacement of some amino acids in the peptide enhanced 100-fold antihypertensive activity (Matoba et al. 2001; Yamada et al. 2002). Miguel et al. (2005) reported RADHPFL, YAEERYPIL and IVF peptides in crude egg white with potent ACE-inhibitory and antihypertensive activities. RVPSL peptide from egg white showed the highest level of ACE inhibitory activity, and QIGLF potential ACE inhibition. Hydrolysate of egg yolk also have ACE inhibitory activity, peptides with 1 kDa or less reduced the hypertension in spontaneously hypertensive rats after 12 weeks (Yoshii et al. 2001; Liu et al. 2010; Yu et al. 2011).

Peptides with antihypertensive activity have been detected in marine species (LKP, IKP, LRP, MVGSAPGVL, LGPLGHQ and AHIII). Also, plants provide antihypertensive peptides, i.e., peptides extracted from oats and barley (IVY and INP) showed strong inhibitory action on ACE. It is important to distinguish between the effect of plant proteins and other components, like isoflavones, phenols compounds and carotenoids on blood pressure levels (Motoi and Kodama 2003; Altorf–van der Kuil et al. 2010; Malaguti et al. 2014; Cheung, Ng, and Wong 2015; Gangopadhyay et al. 2015).

In general, peptides derived from any type of food have significant antihypertensive effect in humans, which has been confirmed by clinical trials in normotensive and pre-hypertensive patients (Cicero et al. 2016).

2.2. Anti-cholesterolemic

The bioactive peptides with clinical evidence of cholesterol lowering effect are found in soybean, lupin and milk proteins; a decrease in total cholesterol (2%), LDL (3%), HDL (3%) and triacylglycerol (4%) has been reported (Lammi et al. 2014; Tokede et al. 2015; Butteiger et al. 2016). Lunasin (a peptide of 43 amino acid) is found in soybean, barley, rye, and wheat and has shown a cholesterol-lowering activity and increasing production of LDL receptors; however, further studies are necessary to assess its efficacy and safety in clinical practice. Protein conglutin, the protein from lupin, lowered effectively LDL-cholesterol in a rat model, and increases LDL receptors in a hepatoma G2 cell line. Besides, peptides from cowpea inhibited cholesterol synthesis (Hernandez-Ledesma, Hsieh, and Ben 2009a; Hernandez-Ledesma, Hsieh, and O De Lumen 2013; Lule et al. 2015; Marques et al. 2015; Sirtori, Arnoldi, and Cicero 2015).

The main mechanism to reduce the serum cholesterol levels is the inhibition of the hydroxymethylglutaril-CoA (HMG-CoA) reductase and the increase in fecal excretion of bile salts. β-lactotensin is a peptide of milk that also lowers cholesterol; it significantly reduced cholesterol in mice at a dose of 100 mg/kg. It probably acts on dopamine D1 and neurotensin NTS2 receptor, which increase the synthesis of bile acids. In summary, the mechanisms of action of the lipid-lowering peptides are mainly by inhibition of the production of endogenous cholesterol and the fecal excretion of exogenous cholesterol (Yamauchi, Ohinata, and Yoshikawa 2003; Lammi et al. 2014; Cicero et al. 2016).

2.3. Antioxidant

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are free radicals produced by endogenous oxidation-reduction (REDOX) reactions, i.e., through normal respiration in aerobic organisms. ROS/RNS are useful to facilitate biological processes such as gene expression, cell proliferation, angiogenesis, programmed cell death, senescence and defense against infections. Under normal conditions, the body antioxidant defense systems can remove reactive species; however, in certain circumstances the endogenous defense system fails, resulting in oxidative stress. When accumulated ROS/RNS exceeds the threshold of the body, cellular damage is induced, which results in macromolecular damage such as atherosclerosis, arthritis, hypertension, cancer, diabetes, neurodegenerative disorders, heart disease, stroke, and aging (Castro and Freeman 2001; Hancock, Desikan, and Neill 2001; Evans et al. 2003; Johansen et al. 2005; Valko et al. 2007; Dowling and Simmons 2009; Scherz-Shouval and Elazar 2011; Liu et al. 2016).

Once the redox balance is interrupted, it is necessary to reinforce the intake of antioxidants from food sources. Vitamin C, herbal extracts and artificial antioxidants have been marketed for a long time as natural antioxidants. However, amino acids and peptides could also provide antioxidant effect to protect cells against oxidative damage. Peptides with antioxidant capacity are safe, healthy, stable and without dangerous immunological reactions (Shahidi 2000; Sarmadi and Ismail 2010).

Antioxidants peptides comprise 4 to 16 amino acids and approximately 400 – 2000 Da molecular weight. Low molecular weight peptides (<3 kDa) present better antioxidant potential than high ones. Small molecules can easily cross the gastrointestinal barrier and enter to peripheral tissue; they can be digested by gastrointestinal proteases, and their antioxidant capacity increases because they can be absorbed more easily (Rubas and Grass 1991; Roberts et al. 1999; Wang et al. 2008; Liu et al. 2010).

Peptides with strong antioxidant activities have been found in crude albumin proteins. The egg white peptide TAQQRTPIL, with ACE-inhibitory activity, also exhibited a high radical-scavenging activity (Davalos et al. 2004; Bhat, Kumar, and Bhat 2017).

2.4. Anti-inflammatory

Inflammation is an important defense mechanism of the body to protect it for infection and injury. The body cells respond to different stimulus by producing inflammatory mediators (eicosanoids, vasoactive amines, vasoactive peptides, lipid mediators, cytokines, chemokines and proteolytic enzymes), which interact with all cells to release inflammatory response. Inflammation is related to a wide variety of diseases, including asthma, ulcerative colitis, Crohn's disease, cancer, type 2 diabetes, cardiovascular diseases (atherosclerosis), and central nervous

system-related disorders (Parkinson's disease and cognitive impairment) (Laveti et al. 2013).

Pharmacological therapies against chronic inflammatory diseases often produce side effects; hence, scientists suggest that the intake of food compounds than can modulate chronic inflammatory conditions. *In vitro* cell and *in vivo* animal studies indicate that peptides from food proteins are safe, without any deleterious side effects and are well recognized by their enormous potential as anti-inflammatory agents (Kovacs-Nolan et al. 2012; Nakamura et al. 2013; Kobayashi et al. 2015; Minihane et al. 2015).

The anti-inflammatory capacity of bioactive peptides is not completely understood. It could be related to the modulation of transcription factors and the inhibition of expression of pro-inflammatory cytokines and chemokines. These peptides are found in different food sources such as bovine milk, egg, fish, and soybean (Cicero et al. 2016; Majumder, Mine, and Wu 2016). Holmer-Jensen et al. (2011) reported a reduction in postprandial inflammation in obese and non-diabetic subjects using milk proteins. Majumder et al. (2013) found a tripeptide from ovotransferrin, albumen of eggs, with anti-inflammatory activity. Peptides derived from soybean, bean and milk have also shown anti-inflammatory effects on intestinal inflammation. Lunasin, a soybean peptide, has also shown anti-inflammatory properties. The most studied peptides with this activity are IPP and VPP, from different sources (Cam and de Mejia 2012; Majumder, Mine, and Wu 2016).

2.5. Anti-carcinogenic

Cancer occurs when some cells in the body ignore growth inhibitory signals, avoid cell death, replicate without limit, sustain angiogenesis and invade tissues, at the end the system fails to eliminate cancer cells. It is one of the major causes of mortality around the world. Radiation and chemotherapy are the principal methods for cancer management; however, both therapies are highly toxic and with some severe side effects. Nowadays, the development of novel tumor-targeted to eliminate tumor cells, in a specific and effective way, with low toxicity, is considered of great importance (Kang et al. 2012; Ortiz-Martinez, Winkler, and García-Lara 2014). On the other hand, the relationship between the risk increasing of colorectal cancer and eating habits, physical activity and obesity is well established (Wolin et al. 2010). Currently, the pharmaceutical industry is developing novel peptides that are more precise to kill cancer cells. Small peptides possess favorable advantages like high affinity, strong specificity, low toxicity, distinct tissue distribution patterns, and good solubility properties, which could ensure high uptake into target tissues and rapid clearance from the blood and non-target tissues. The explorations and modifications of anticancer peptides will play important roles in cancer prevention and treatment (Shadidi and Sioud 2003; Bhutia and Maiti 2008; Chen and Conti 2010; Lee, Xie, and Chen 2010; Segura-Campos et al. 2011; Wu et al. 2014).

Bioactive peptides derived from plants, animals, milk, eggs, marine organisms and microorganism, could be utilized against some cancer types due to their effect on one or more carcinogenesis molecular pathways. Bioactive peptides present different mechanism of action, i.e., apoptosis, blockage of intermediate tumor generation and regulation of immune system, inhibition of cell migration and tumor angiogenesis, antioxidant activity, inhibition of cell proliferation, tubulin structure disorganization and cytotoxicity (Schweizer 2009; Thundimadathil 2012; Tyagi et al. 2014; Blanco-Míguez et al. 2016).

In vitro studies on lunasin have confirmed anti-neoplastic effects in breast, skin, colon, prostate, leukemia and lymphoma cell lines. Besides, the pentapeptide EGRPA of rice bran, at a dose of 600–700 μg/mL, inhibited the 84% of the growth of colon cancer cells (Caco-2 cell line and human colorectal adeno-carcinoma, HCT-116), 80% in breast cancer (MCF-7 and MDA-MB-231) and 84% in liver cancer (HepG-2 cells) (Hsieh, Hernández-Ledesma, and De Lumen 2010; Kannan et al. 2010; Diaz and de Mejia 2011; Chang et al. 2014; Hernandez-Ledesma and Hsieh 2017).

Bowman-Birk inhibitor (BBI), a bioactive peptide of legume seeds, is a source of protease inhibitors and has preventive effect against prostate, breast and colon cancer, and could be an effective suppressor of carcinogenesis. The use of BBI in patients with benign prostatic hyperplasia was approved by the Food and Drug Administration (FDA); patients show tolerance for a prolonged period of time (Armstrong et al. 2000; Malkowicz et al. 2001; Park, Jeong, and De Lumen 2005).

Lectins, plant derived peptide, are able to recognize specific carbohydrates produced by malignant cells or tissues. Lectins show antiproliferative and cytotoxic effects by inhibiting colony formation on cervical and human colon carcinoma cell lines. They also showed, in a mouse model, an immunomodulatory effect that delayed the development of colon cancer and improved the survival of mice with leukemia cells (Ma et al. 2008; Seifert et al. 2008; Valadez-Vega et al. 2011).

Lactoferrin, a whey protein, inhibits the growth of nasopharyngeal carcinoma and breast (MDA-MB-231) cancer cells. These effects were confirmed with an *in vivo* model, in addition this protein can inhibit spontaneous growth of melanoma cells and suppresses metastasis of liver and lung lymphoma. Lactoferrin acts against different types of cancer cell lines, by inducing apoptosis, modulating gene expression, preventing angiogenesis and disorderly growth of the cells, and stopping the cell cycle. Another whey protein, α-lactalbumin, activated apoptosis *in vitro* chemoprevention. In milk two peptides derived from casein β-casomorphin 5 showed the capacity to arrests the cell cycle in breast cancer cells and induce apoptosis in HT-29 and AZ-97 (Hatzoglou et al. 1996; Yoo et al. 1997; Damiens et al. 1999; Varadhachary et al. 2004; Fast et al. 2005; de Mejia and Dia 2010; Perego et al. 2012; Sun et al. 2012; Deng et al. 2013).

Some egg-derived peptides like hydrolysates from egg yolk protein, lysozyme and ovomucin, have shown anticancer properties. *In vivo* studies demonstrate that hydrolysates from egg yolk protein inhibit the proliferation of tumor cells in colorectal cancer; lysozyme reduces the formation of lung metastases of B16 melanoma and ovomucin inhibits tumor growth(Watanabe et al. 1998; Azuma et al. 2000).

Some bioactive peptides derived from different marine species, induce antiproliferative activity against different cancer types. *In vitro* assays showed positive effect of tuna dark muscle peptides on human breast cancer cells; also besides, peptides

from squid gelatin had cytotoxic activity on human breast carcinoma (MCF-7) and glioma cell lines, and peptide reniochalistatin E from the sponge *Reniochalina stalagmites* showed cytotoxic activity toward several tumor cell lines. On the other hand, peptides called BEPT II, BEPT II-1, Dolastatins and Pardaxin induced apoptosis toward different types of cancer (Bai, Petit, and Hamel 1990; Anderson et al. 1996; Alemán et al. 2011b; Hsu, Li-Chan, and Jao 2011; Ma et al. 2013; Ting et al. 2014; Zhan et al. 2014). Additionally, *in vivo* studies confirmed that the polypeptide P2 of *Arca subcrenata* has an antiproliferative action on HeLa and HT-29 cells in S-180 tumor-bearing mice, and peptides from oyster (*Crassostrea gigas*) showed an antiproliferative effect against sarcoma-S180 in mice (Wang et al. 2010; Hu et al. 2012).

Bioactive peptides possess outstanding characteristics to produce anti-tumor drugs, like high selectivity, wide range of targets and low toxicity; however, they present some problems, such a poor stability, low membrane permeability and susceptibility to proteolytic digestion. In order to avoid these difficulties, some modifications have been developed, i.e., amino acid substitution, structural fusion of functional peptides and conjugation with chemotherapeutic drugs (Vlieghe et al. 2010; Zhang, Eden, and Chen 2012; Craik et al. 2013; Wu et al. 2014).

2.6. Anti-microbial activity and immunomodulatory effect

The immune system represents the first line of defense against infections, and its optimum performance is vital to provide protection. Innate immunity is mainly represented by different cells, including dendritic, macrophages and natural killer (NK); some immune stimulants increase the activation of these cells (Akira, Uematsu, and Takeuchi 2006).

Over the years, anti-microbial plant derived peptides have become interesting tools for the production of new antibiotics for the treatment of different infections. This kind of peptides are obtained from various sources and are the first line of defense in animals. These peptides contained different amino acids positively charged such as arginine, lysine, histidine, and an excess of glutamic and aspartic acids negatively charged. They usually disintegrate the cell membrane by altering its permeability (Kitts and Weiler 2003; Otvos Jr 2016).

Lactoferrin, protein fraction from human and bovine milk, tuna and sardine meat, barley, and pumpkin, is produced in Japan. It is considered a potent anti-microbial and also is used in the prevention of infections and the improvement of bowel flora of milk-fed infants and in other health conditions (Bellamy et al. 1992; Nayak et al. 1999).

Some plants produce anti-microbial peptides involved in defense against infection or natural invaders. Thionins are basic peptides identified in wheat, barley, rye and oats. They are homologous polypeptides with 43–46 amino acid, rich in cysteine and lysine residues. Thionins have anti-microbial activity against plant pathogenic fungi and bacteria (García-Olmedo et al. 1998; Kitts and Weiler 2003). Small peptides from maize kernels showed anti-microbial properties; they were similar to thionins and one was purified, MBP-1, with 33 residues and 4127 Da (Duvick et al. 1992).

Immunomodulatory peptides do not target the pathogen directly; however, they can enhance host defense mechanisms by activating immune cell functions, like lymphocyte proliferation, natural killer cell activity, antibody synthesis and cytokine regulation; besides, they might reduce allergic reactions in atopic humans and enhance mucosal immunity in the gastrointestinal tract (Korhonen and Pihlanto 2003; Fitzgerald and Murray 2006; McCann et al. 2006; Hartmann and Meisel 2007; Mookherjee and Hancock 2007). For example, some casein peptides stimulated phagocytes and the production of IgG in lymphocytes, as well as the proliferation of T lymphocytes. On the other hand, fish peptides presented immunomodulatory effects in animals, and oyster hydrolysates increased the activity of natural killer cells. Peptides obtained from rice and soybean proteins activated the defense systems, and stimulated anion superoxide (ROS), which activated non-specific immune defense systems (Cheung et al. 1980; Lahov and Regelson 1996; Hata, Higashiyama, and Otani 1998; Kitts and Weiler 2003; Yang et al. 2009; Wang et al. 2010; Cheung, Ng, and Wong 2015).

Hypothetically, immunopeptides interact on the opioid receptors that regulate the peripheral immune system. In addition, peptides with arginine, tryptophan and phosphoserine in the N or C terminal residues exert high reactivity in immune cells. In addition, glutamine residues involved in the recognition of opiod receptors are located on the surface of immune cells (Elitsur and Luk 1991; Mookherjee and Hancock 2007; Haque, Chand, and Kapila 2008; Santiago-López et al. 2016).

3. Maize

Maize (*Zea mays* L.) is one of the most important grains originated in the New World. It was the main food for different pre-Columbian societies in America, and was domesticated approximately 6000–10,000 years ago. In the Mayan culture, maize was as important that was used in spiritual and religious rituals (Piperno and Flannery 2001; Matsuoka et al. 2002) (http://maize.teacherfriendlyguide.org/index.php/what-is-maize/cultural-uses-of-maize). Maize is native to Central Mexico and several studies indicate that annual teosinte (*Zea mays* ssp. *parviglumis*) was its predecessor in at least two separate domestication sites in Mexico. Isoenzymes, molecular and cytological data, indicate that wild maize is native to the Balsas River Valley in Michoacan and Guerrero, Mexico. However, another theory argues that it is native to Tehuacan, Puebla, Mexico (Piperno and Flannery 2001; Matsuoka et al. 2002; Wu et al. 2008; Somerville et al. 2016; Orona-Tamayo and Paredes-López 2017a; Orona-Tamayo, Valverde, and Paredes-López 2017b).

3.1. Nutritional composition

Maize is one of the world's three main cereal crops and is consumed by millions of people specially from the developing countries. The main parts of the maize kernel are the endosperm and germ; both tissues contain most of the starch (62%) and oil (3.8%). The protein content is 6 to12% and almost 75 to 80% is in the endosperm, the rest is found in the germ and bran. The proportion of endosperm protein fractions is 3 to 12% for albumins, 3 to 10% for globulins, 38 to 60% for prolamins or zeins, and 25 to 40% for glutelins. Zeins are well balanced with glutamine (20%), leucine (20%), alanine (14%),

proline (9%) and serine (7%); but lack of two important essential amino acids, lysine and tryptophan. In 1960, efforts were made to increase the nutritional quality of maize protein. The high proportion of zeins is related to the poor quality of protein; hence research studies have focused on the reduction of this fractionin order to increase other fractions with more lysine and tryptophan content (Dierks-Ventling 1981; Larkins et al. 1984; Vasal 2000; Shukla and Cheryan 2001; Rascón-Cruz et al. 2004).

3.2. Bioactive peptides

Zein peptide LPP shows strong ACE inhibitory activities, and have applications in the medical field for lowering blood pressure (Table 3) (García et al. 2013; Corradini et al. 2014). Maruyama et al. (1989) reported that the native sequence VHLPPP from ɣ-zein had stronger antihypertensive effect in spontaneously hypertensive rats than synthesized peptides. Similarly, Miyoshi et al. (1991) found *in vitro* that antihypertensive tripeptides isolated from α-zein hydrolysates with thermolysin (LGP, LSP and LRP) showed similar ACE inhibitory activities; however, the LRP peptide showed the strongest inhibition effect on blood pressure in spontaneously hypertensive rats. (Puchalska, Marina, and García 2012; 2013) found significant differences in the content of these three Zein peptides in diverse maize lines (Table 3). Ren et al. (2014) found that sweeping frequency ultrasound (SFU) treatment of zein increased hydrolysis, and the hydrolysates presented a higher inhibition effect on ACE. It shows that the use of this methodology promotes the release of ACE-inhibitory peptides from zein by altering the secondary structure and loosening the protein.

Kong and Xiong (2006) reported that hydrolyzed zein is an excellent antioxidant and also possesses a strong chelating activity against Cu^{2+}, as well as strong reducing power. Although intact zein displayed antioxidant effect, it was far less potent than the hydrolyzed zein peptides. Tang et al. (2009) separated zein hydrolysates by gel filtration, ultrafiltration, and reversed-phase HPLC, and concluded that peptides of <1 kDa exhibited a strong DPPH, ABTS and O_2^- scavenging activity. They also purified and identified two peptides (YA, and LMCH) exhibiting high antioxidant reactivity.

Several small peptides with antimicrobial properties have been isolated from maize kernels. Duvick et al. (1992) found a 4.1 kDa peptide with antimicrobial properties, named MBP-1, similar to thionins. MBP-1 inhibits spore germination and the hyphal elongation of several plant pathogenic fungi (*Fusarium montiliforme* and *F. graminearum*) and maize phytobacteria such as *Clavivacter michiganense*. Wound infection is a common problem in hospitals and it is typically caused by the antibiotic-resistant *Staphylococcus aureus*, which is the major pathogen for skin and soft tissues infections. Salouti et al. (2016) investigated the antibacterial effect of MBP-1 peptide in combination with silver nanoparticles on infected wounds caused by *S. aureus* in animal models, and found that this combination increased wound healing rates and decreased colonization of *S. aureus*. Sousa et al. (2016) identified antibacterial activity in MBP-1 and concluded that by replacing cysteine and tryptophan can abolish this activity against gram negative and positive bacteria.

3.3. Genetic engineering to improve the functional properties of peptides

In maize seeds, different studies have been performed to elucidate genes encoding storage proteins. These genes are under strict control and are expressed in a tissue specific manner. The zein protein fraction is loaded with a high amount of bioactive peptides, and is a great blank to transform different plants (Yamamoto, Ejiri, and Mizuno 2003; Sarmadi and Ismail 2010). From the middle of the 1960s, great efforts were performed to improve the nutritional quality of the maize endosperm proteins with the mutant lines of opaque-2 and floury-2. These mutants alter the amino acids compositions of maize endosperm proteins, two-fold increase in levels of lysine and tryptophan; and other amino acids such as histidine, arginine, aspartic acid, and glycine are also increased. These mutations affect some agronomic performance including yield and consumer aspects of the kernel. Subsequently, several other mutant genes in maize have been discovered such as opaque-7, opaque-6 and floury-3; these mutants reduce the zein content and increase lysine and tryptophan levels due to synthesis of non-zein proteins such as glutelins, globulins and albumins. These studies were focused to improve the nutritional quality resulting in the Quality Protein Maize, hybrids that gained at the beginning certain popularity in development countries (Huang et al. 2004).

In the 80s, the high potential to produce transgenic plants with the expression of chimeric genes transferred into plants cells via *A. tumefasciens*. This technology led to researchers to obtain transgenic plants with a high level of essential amino

Table 3. Bioactive peptides from maize (Zea mays).

Bioactive function	Protein source	Bioactive Peptide/Peptide sequence	Reference
Antihypertensive	Zein (Prolamin)	LPP	Corradini et al. 2014; García et al. 2013
	ɣ-Zein (Prolamin)	VHLPPP	Maruyama et al. 1989
	α-Zein (Prolamin)	FNQ, FSQ, LAY, LNPA, LSPA, AF, LPN, FYQQ, YLEPA, FY, LSPY, LNSPAY, LLP, LF, FLP, LVP, FLPP, LQQ, YSQQQQ, FNQ, ASY, AY, AYPQQ, LSPQSY, LSLP	Yano, Suzuki, and Funatsu 1996
	α-Zein (Prolamin)	LQP, LSP, LRP	Miyoshi et al. 1991; Puchalska, Marina, and García 2012; Puchalska et al., 2013
Antioxidant	Zein	YA, LMCH	Tang et al. 2009
Antimicrobial	Total protein	RSGRGECRRQCLRRHEGQPWETQECMRRCRRR	Duvick et al. 1992; Sousa et al. 2016

See Table 2 for the amino acid nomenclature used in this table.

acids with the introduction and expression of maize zein gen. Matzke et al. (1984), reported the first evidence for transcription of a genomic clone of maize zein introduced with T-DNA into sunflower cells; they found that the zein mRNA made in sunflower can be translated *in vitro* to yield an immunoprecipitable protein with expected molecular weight as native zein in maize. Moreover, transformed tobacco plants were developed containing maize gene encoding a zein protein using a modified Ti plasmid vector; zein proteins were detected in roots, leaves and endosperm tissues. In addition, constructed chimeric genes containing a maize α-zein coding sequence and a β-phaseolin gene promoter and were inserted into genome of tobacco plants via *A. tumefasciens* transformation. α-zein mRNA in tobacco seeds varied between 1.0 and 2.5% of total mRNA; the α-zein protein was immunologically detected in seed extracts of transgenic plants (Schernthaner, Matzke, and Matzke 1988; Ohtani et al. 1991). These genetic efforts may enrich some plant products by increasing the concentration of selected bioactive peptides.

4. Common bean

Phaseolus vulgaris species or common beans are native to Mexico and Guatemala, and were associated with the development of the pre-hispanic cultures and today they play an important role in the nutrition of an important part of the world's population. They represent more than 50% of the legumes that are used for human consumption worldwide, which is due to its outstanding nutritional content sensorial properties and health effects. Beans are a major source of highly valuable plant protein, dietary fiber and micronutrients and are associated to lowering the risk of non-transmissible sicknesses, including diabetes and cardiovascular diseases, lowering blood glucose and lipid levels, decreasing cholesterol and triglycerides, as well ascertain benefits against cancer, and the treatment of obesity and metabolic syndrome. Some legume seeds also have anti-tumor, antiviral and antifungal activities (de Mejia et al. 2005; Wang, Rao, and Ye 2009; Lam and Ng 2011; Campos-Vega et al. 2012; Olmedilla−Alonso et al. 2013; Romero-Arenas et al. 2013; Rubiales and Mikic 2015). On the other hand, common beans have a key role in the diversification and intensification of agriculture by contributing to improve the environment due to their biological nitrogen fixation, effects on the soil, and control of weeds (Rubiales and Mikic 2015).

4.1. Nutritional composition

Common beans are rich in carbohydrates (60%) and proteins (19–27%), as well as a good source of vitamin B complex such as niacin, riboflavin, folic acid and thiamine; they also comprise iron, copper, zinc, phosphorus, potassium, magnesium and calcium. Besides, they have high fiber content and are an excellent source of polyunsaturated fatty acids. Phaseolin (30.2 to 53.5% of the total protein) is the principal storage protein and the most abundant protein in common beans; it has high resistance to proteolysis due to its globular and glycosylated structure (Montoya et al. 2010). *P. vulgaris* proteins are excellent source of bioactive peptides, which provide antioxidant, antihypertensive, anticancer and antiinflammatory activities. On the other hand, common beans have phenolic acids, flavan-3-ols, flavonols, flavanones and anthocyanidins that showantioxidant, antiinflammatory, antihypertensive and antiatherosclerotic properties (Lin et al. 2008; del Rio et al. 2013; Romero-Arenas et al. 2013; Luna-Vital et al. 2015).

4.2. Bioactive peptides

Common bean protein is a low cost source for bioactive peptides and a great alternative as nutraceutical product or functional ingredient. Garcia-Mora et al. (2016) reported several ACE-inhibitory and antioxidant peptides in Pinto beans through BIOPEP Database; and concluded that the small peptides (<3 kDa) were the main contributors in these activities as well as specific amino acids in the peptide sequence; however, some peptides had more than one potential biological activity as a result of the amino acid sequences. Tagliazucchi et al. (2015) identified ACE-inhibitory peptides after gastrointestinal digestion of Pinto bean; they were di- or tri- peptides and the majority had a hydrophobic amino acid, (iso) leucine or phenylalanine, or proline at the C-terminal position which is crucial for the ACE-inhibitory activity. (Mojica and González de Mejia 2015) and Luna-Vital et al. (2015) concluded that ACE inhibition is the most frequent biological function of bean peptides (87.5%); they also reported DPP-IV inhibition in more than half of sequences analyzed (74 peptides), important in type-2 diabetes treatment and antioxidant capacity (36 sequences). On the other hand, Mojica and González de Mejia (2016) established a systematic evaluation and characterization for anti-diabetic peptides from black bean protein and found that peptides EGLELLLLLAG, AKSPLF and FEELN inhibited DPP-IV more efficiently than the control, and TTGGKGGK had higher inhibitory potential on α-glucosidase compared to the control acarbose. (Oseguera-Toledo, De Mejia, and Amaya-Llano 2015) also reported, peptides that inhibit *in vitro* α-amylase and α-glucosidase. Mojica, Luna-Vital, and Mejía (2017) found that phaseolin remained almost unhydrolyzed after digestion with pepsin/pancreatin; they also found four peptides: KKSSG, KTYGL, GGGLHK and CPGNK with potential to inhibit DPP-IV, ACE and α-glucosidase enzymes. Besides, they concluded that the biological activities are related to small amino acid sequences and demonstrated significant antioxidant, antidiabetic and antihypertensive properties (Table 4).

Wang and Ng (2007) found a 7.3 kDa peptide from *P. vulgaris* with potent antiproliferative activity for leukaemia cell line L1210 and lymphoma cell line MBL2. Luna-Vital et al. (2015) reported five peptides (GLTSK, LSGNK, GEGSGA, MPACGSS and MTEEY) in non-digestible fractions of common bean with antiproliferative activity on human colon cancer cells, that were produced by modifying molecules involved in cell cycle arrest or apoptosis. On the other hand, Lam and Ng (2011) reported that hemagglutinin from *P. vulgaris* protein, suppressed the proliferation of breast cancer MCF-7 cells (IC_{50} of 0.2 μM), and induced cell cycle arrest in G2/M phase, phosphatidyl serine externalization, mitochondrial membrane depolarization and apoptosis by activating the death receptor-mediated pathway.

Table 4. Bioactive peptides from common beans (*Phaseolus vulgaris*).

Bioactive function	Bioactive peptide sequence	Reference
Antihypertensive	KKSSG	Mojica, Luna-Vital, and Mejía 2017
	KTYGL	
	GGGLHK	
	CPGNK	
	LSFNT	
	KMARPV	
	GHVPP	
Antioxidant	TACKD	Mojica, Luna-Vital, and Mejía 2017
	GGGLHK	
	KTYGL	
	MPHLK	
Antidiabetic	EGLELLLLLLAG	Mojica and De Mejia 2015
	AKSPLF	Luna-Vital et al. 2015
	FEELN	Mojica and De Mejia 2016
	TTGGKGGK	Mojica, Luna-Vital, and Mejía 2017
	KKSSG	
	KTYGL	
	GGGLHK	
	CPGNK	
	VKFMT	
Anticancer	GLTSK	Luna-Vital et al., 2015
	LSGNK	
	GEGSGA	
	MPACGSS	
	MTEEY	

See Table 2 for the amino acid nomenclature used in this table.

4.3. Genetic engineering to improve the functional properties of peptides

The global economic importance of bean is due to mainly their high amount of storage proteins. In contrast to other legume seeds, common beans are composed of high amounts of globulins or phaseolin (7S fraction). Phaseolin contains different bioactive peptides encrypted in its amino acid sequence, and is coded by a multigene family; their expression is temporally regulated during embryogenesis and is localized in the embryonic tissues of common bean; from the 80's this protein fraction has been under several studies to improve the nutritional properties in different plants (Slightom et al. 1985; Chappell and Chrispeels 1986; Montoya et al. 2010; Carrasco-Castilla et al. 2012). Murai et al. (1983) transformed sunflower tissue cell with sequences coding phaseolin protein from common bean, consequently the protein was detected in transformed cells with different biochemical tools.

Similarly, Bustos et al. (1991) transformed tobacco plants with four phaseolin genes, the specific phaseolin mRNA was similar to those found in plants transformed with a bean genomic DNA sequence that encodes an identical β–phaseolin subunit. In addition, Bagga et al. (1992) introduced a chimeric β–phaseolin gene into alfalfa plants to study the pattern of accumulation of this protein in different parts of the transgenic plant including the mature seeds. They found high concentrations of phaseolin transcripts, however mature seeds only presented significant accumulation of the phaseolin protein. Zheng et al. (1995) expressed phaseolin in the endosperm of transgenic rice plants; promoter fragments of the rice glutelin gene were fused transcriptionally to either genomic or cDNA of phaseolin gene. These studies demonstrated the expression of a phaseolin gene derived from common beans transferred to improve the nutritional properties to distinct taxonomically plant species.

Many legume seeds are deficient in one or more essential amino acids, and improving the sulphur-containing amino acids has been a challenge for different research groups (Montoya et al. 2010). It is well known that common beans have a low content of sulphur-containing amino acids (Evans and Bandemer 1967); there is a great interest by plant breeders in increasing its methionine content. Protein engineering has offered alternatives for manipulating the amino acid content in the phaseolin. In this sense, (Dyer, Nelson, and Murai 1993) utilized molecular mechanic calculations to evaluate several strategies for improving the nutritional seed quality; these authors used this structure to simulate modifications aimed at increasing the methionine content of phaseolin. As a result of this simulation, methionine content was increased by the replacement of hydrophobic amino acids with methionine in the central structure of the phaseolin protein. Experimentally, researches have attempted to correct the methionine-deficiency by the introduction of a transgene coding for a methionine-rich storage albumin (2S albumin) from Brazil nut via biolistic methods that derived in bean transgenic lines (Aragão et al. 1992; Aragão et al. 1996; Aragão et al. 1999). Aragão et al. (1992) reported the transient expression of the Brazil nut 2S-albumin gene in cells of the bean embryonic that derived in transgenic bean plants containing and expressing the 2S-albumin gene (Aragão et al. 1996); in addition, the same authors found that in two of the five transgenic plants the methionine content was significantly increased by around 14–23% over the values found in non-transformed plants (Aragão et al. 1999).

The knowledge acquired about two extensively studied storage proteins, γ-zein of *Z. mays* and phaseolin of *P. vulgaris*, has been used to create a fusion protein called zeolin which has the solubility and assembly properties of wild-type γ–zein (Bellucci et al. 2007). Hoffman et al. (1987) used the maize zein gene under regulation of common bean β-phaseolin gene at flanking regions; *A. tumefaciens*-mediated transformation was used to insert the chimeric phaseolin-zein gene into tobacco genome, which gave as a result transgenic plants synthetizing zein in roots, hypocotyls, and cotyledons of germinating transgenic tobacco seeds. Similarly, Mainieri et al. (2004) produced a chimeric protein with the entire phaseolin coding sequence gene fused to the N-terminal region of γ-zein (including the tandem repeated and the Pro-rich domains). While γ-zein and phaseolin usually accumulate in the ER and in storage vacuoles, respectively; in transgenic tobacco leaves, zeolin is retained in the ER where its accumulation in protein bodies can reach 3.5% of the total leaf protein content. Similarly, zeolin was introduced to transform alfalfa plants, and the chimeric protein was expressed and was stably accumulated in alfalfa leaves because it forms endoplasmamic reticulum-located protein bodies in cells (Bellucci et al. 2007). The authors conclude that the γ-zein portion is sufficient to induce the formation of protein bodies when fused to another protein as well. Because the storage proteins of cereals and legumes nutritionally complement each other, zeolin can be used as a starting point to produce nutritionally balanced and highly stable chimeric storage proteins (Mainieri et al. 2004).

5. Amaranth

Amaranth is a dicotyledonousC4plant. It grows fast in soil low in nutrients, and is resistant or tolerant to extreme conditions,

changes of temperature and radiation, which is due to its high osmotic adjustment capacity (Montoya-Rodríguez et al. 2015; Orona-Tamayo and Paredes-López 2017a). Amaranth plants are also widespread in temperate and tropical areas, and there are three main amaranth species native to the New World: *Amaranthus hypocondriacus* from the northwestern and central area of Mexico, *A. caudatus* from the Andes, and *A. cruentus* from the southern Mexico and the central region of Guatemala. Aztec civilizations planted *A. hypochondriacus* as one of their basic foods, Maya and Inca civilizations used *A. cruentus* and *A. caudatus*, respectively. These civilizations used its grains and leaves in different form; i.e., drinks, sauces that were mixed with maize to prepare tortilla, medicinal treatments and also in religious practices. It is worth to mention that amaranth was prohibited by Spaniards conquerors who were scornful of its use in native religious ceremonies (Kauffman 1992; Mallory et al. 2008; Mlakar et al. 2010; Pavlik 2011; Rastogi and Shukla 2013; Orona-Tamayo and Paredes-López 2017a).

5.1. Nutritional composition

The recent agronomic uses of amaranth began in1970 when some researchers found that it was a promising plant; they increased the interest on this crop as potential staple food due to its high-quality proteins and outstanding nutritional compounds (Tucker 1986; Paredes-López 1994). The proximate composition of amaranth seeds depends to certain extent on the specie and culture place. The seed contains a high amount of digestive proteins; total protein ranges from 13.2 to 18.4% comprising a good balance of essential amino acids, close to the optimum required in the human diet. Amaranth contains important amount of crude fiber with ranges from 2.2 to 5.8%; the lipid level ranges between 1.9 and 13.0%, and it is composed by different fatty acids being the most abundant linoleic (36.7 to 55.9%), followed by oleic (18.7 to 38.9%) and palmitic (19.1 to 23.4%) acids. The main carbohydrate is starch (57–62.0%), and sucrose, glucose, raffinose, fructose, staquiose, maltose, and inositol are found in lower concentration. The grain is a good source of minerals such as Ca, Fe, Mn, Mg, K, P and Na. Also contains B complex vitamins. In addition, amaranth has other important bioactive compounds that include diverse metabolites such as phenolic acids, flavonoids, anthocyanins, tannins, and phytosterols (Becker et al. 1981; Segura-Nieto, Barba De La Rosa, and Paredes-López 1994; FAO 1985; Pasko et al. 2008; Repo-Carrasco-Valencia et al. 2009; Alvarez-Jubete, Arendt, and Gallagher 2010a; Ferreira and Areas 2010).

Amaranth contains proteins of high quality. Globulins are the main fraction at the storage proteins, and the most abundant are the 11S and 7S globulins. The 11S globulin, known as amarantin, has similar function as legumins, a molecular weight of 300–400 kDa and six subunits of 50–60 kDa. 7S globulins comprise four subunits (66, 52, 28 and 16 kDa) which integrate a polypeptide of 150–200 kDa. Amaranth globulins show a high concentration of lysine (5.7%) and high levels of sulfur amino acids (5.1%). 11S globulins contain important amounts of methionine (1.7%) and tryptophan (1.6%), high levels of lysine (4.3%), histidine (2.6%), phenylalanine (6.9%), valine (6.3%) and isoleucine (5.0%); while 7S globulin shows low levels of some essential amino acids, such as tryptophan (0.4%) and methionine (0.5%), lysine (3.4%), histidine (1.5%), phenylalanine (4.9%), valine (5.5%), and isoleucine (6.2%) (Paredes-López, Mora-Escobedo, and Ordorica-Falomir 1988; Bressani and Garcia-Vela 1990; Barba de la Rosa et al. 1992; Segura-Nieto, Barba De La Rosa, and Paredes-López 1994; Vasco-Méndez and Paredes-López 1994; Barba de La Rosa et al. 1996; Marcone 1999a; Marcone 1999b; Tovar-Pérez et al. 2009; Quiroga et al. 2010)

5.2. Bioactive peptides

Most of the amaranth proteins encrypts mainly peptides with antihypertensive effect (Table 5). Montoya-Rodríguez et al. (2015) reported that 15 proteins mostly presented ACE-inhibitory peptides, and Fritz et al. (2011) evaluated *in vitro* and *in vivo* ACE-inhibition in peptides from *A. mantegazzium* and *A. hypochondriacus*. Montoya-Rodríguez et al. (2015) reported that50% of peptides from amarantin have ACE inhibitory activity. Besides, Silva-Sánchez et al. (2008) found di- and tripeptides in globulins and glutelins with a strong inhibitory effect against ACE. Tovar-Pérez et al. (2009) identified important ACE-inhibitory effects in peptides from albumin (40%) and globulin (35%) fractions from *A. hypochondriacus*. Moreover, Vecchi and Añon (2009) studied tetrapeptides from 11S globulin of *A. hypochondriacus* with ACE-inhibitory activities (Table 5).

Luna-Suárez et al. (2010) modified the acidic subunit of the 11S globulin from amaranth through the insertion of four peptides with antihypertensive functions. These peptides showed a high inhibition effect against the ACE, eight-fold more than the non-modified 11S globulin. In our laboratory, these peptides were overexpressed in *E. coli* strains to obtain a highly production of antihypertensive peptides (Arano-Varela, Dominguez-Dominguez, and Paredes-López 2012; Castro-Martínez, Luna-Suárez, and Paredes-López 2012; Morales-Camacho, Dominguez-Dominguez, and Paredes-López 2013). Later, these antihypertensive peptides were evaluated by Medina-Godoy et al. (2013) in spontaneously hypertensive rats, and they found considerable reduction of arterial pressure, similar to the control group treated with commercial captopril. Amaranth 7S globulin also encrypts antihypertensive peptides with high ACE-inhibitory capacity (Quiroga et al. 2012). (Barba de la Rosa et al. 2010) reported that peptides from amaranth glutelins possess various amino acids with high ACE-inhibitory effects, comparable to captopril.

Qureshi Lehmann, and Peterson(1996) assessed the influence of amaranth in the cholesterogenesis in chickens of 6 weeks of age and found that it reduced total and LDL-cholesterol; also, they concluded that cholesterol-7-alpha-hydroxylase enzyme and3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) decreased. Similarly, Plate and Arêas (2002) reported a reduction in LDL and total cholesterol in hypercholesterolemic rabbits supplemented with extruded amaranth; they suggested that amaranth consumption may be an alternative option to prevent coronary diseases. However, these studies attributed the anti-cholesterolemic effects to different compounds, such as fiber and the bioactive peptides encrypted in the protein sequences. On the other hand, Escudero et al. (2006) reported that Winstar rats fed with concentrates of amaranth protein

Table 5. Bioactive peptides from Amaranth (*Amaranthus hypochondriacus*).

Bioactive function	Protein source	Bioactive Peptide/Peptide sequence	Reference
Antihypertensive	Total protein (hydrolysates)	YL, RW, RR, KL, LF, EG, GT, HK, RP, HP, PG, GG, GL, LG, GA, AG, GT,HG, FG, PR, GP, PRY, DG, GP,	Montoya-Rodríguez et al. 2014
	Albumin	AG, GL, RY, LQ, LA, EV, VE, RW, LY,EG LG, GH, TE, VG, GG, GS, TG, VF,IF, TF, KG, NG, GK, GV, FG, GY, YG, LN, AH, MF,GT, KF, PR, EA, AA, FR,KR, SG, TQ,AI, EI, IE, RL	Montoya-Rodríguez et al. 2015
	Amarantin (11S globulin)	GKP,LF,FP,YL,RF,HY,VYV ALEP,VIKP VY	Silva-Sánchez et al., 2008 Vecchi and Añon 2009 Luna-Suárez et al. 2010; Arano-Varela, Dominguez-Dominguez, and Paredes-López 2012; Castro-Martínez et al., 2012; Morales-Camacho, Dominguez-Dominguez, and Paredes-López 2013; Medina-Godoy et al. 2013
		SG, GF, HP, PT, NG, MG, GE, EG, GR, FR, QG, GL, TE, EV, AG,GV, RR, IE, PH,HG, AP, IY, GI, TG, GM, IP, PG,GS, GG, KF, FG, GD, HL, IF, EA, AA, KG, LY, LN, AH,MY, GQ,VF, VP,AI, AF, EW,MF,RL, IR, IKP, GKP, IEP, ALEP,	Montoya-Rodríguez et al. 2015
	7S Globulin	DA,GK,QG,LQ,RL2VF,PR,PL,AP,GF,FR,VG,AG,2 GE,MGGK,GD,EG,EA,2LQ,LN,PQ,EW,HP LVL,HY,FP,PR,4LF,GPL,2GP,PL,VK,2AF,2LA,KR, VP,3FR, GL,GH,GR,2FG,GK,GT,GG,2EG,NG, 2PG,VR,GHF,NY,NF,2LQ,LN,EK VLP,LNP,2YL,GPL,PL,AF,AP,3GA,3AG,2FG,GS,2 GV,2GT,QG,4SG,GHF,RR,AR,PH,2VF,GY,AY,AA, VG, GE, QG, EA, NG, NF, YK, EV 2LY,LVL,RF,Hy,GY,LNP,YL,2LF,VK,2AF,AP,2LA, FR,GA,3GL,GR,FG,GS,GT,2SG,2LG,2EG,NY,2 SF, KL, LVE, VE, LQ, LN, TQ, EK. KE, PH LP, RL, PR, LSP, LF, FFL, VP, GF, AG, SY, LN, PQ, TF, EL, FA, LP, VLP, VF, HY, GY, AF, LA, KR, FR, VG, 2 NF VF, FP, GF, GL, FG, LN, HY, PR, LF, GP, AF, LA, KR, PG, NF	(Quiroga et al. 2012
	Glutelin	AP, AIP, ALPP, AVP, AY, FNQ, FP, FQP, FY, GGY, GKP, GRP, GY, HIR, HY, IKP, ILP, IR, IRA, IY, LAA, LAMA, LAY, LF, LLP, LNP, LPP, LQP, LQQ, LRP, LSP, LVL, LVR, LW, LY, MF, MY, PLP, PQR, PR, PRY, RF, RL, RY, TAP, VAA, VAP, VAY, VF, VLP, VPP, VRP, VSP, VW, VY, VYP, YG, YGGY, YL, YP	Silva-Sánchez et al. 2008
		AY, FP, FY, GY, HY, IR, IY, LF, LW, LY, MF, MY, PR, RF, RL, RY, VF, VW, VY, YG, YL, YP AAP, AIP, AVP, FNQ, FQP, GGY, GKP, GRP, HIR, IKP, ILP IRA, LAA, LAY, LLP, LNP, LPP, LQP, LQQ, LRP, LSP, LVL, LVR, PLP, PQR, PRY, TAP, VAA, VAP, VAY, VLP, VPP, CRP, VSP, VYP, ALPP, LAMA, YGGY	Barba de la Rosa et al. 2010
Antioxidant	Total protein (hydrolysates)	PYY, RWY, WY, RW, PWW, PWR, PW, PWY, WYS, PW, WY	Montoya-Rodríguez et al. 2014
	Albumin	LK, TY, RW, LH, KP, EL, LHV, LVR	Montoya-Rodríguez et al. 2015
	Amarantin (11S globulin)	IR, EL, TY, HL, YL, LH, KP, VY, LK, PHG, PEL, RHL, LHV	Montoya-Rodríguez et al. 2015
		AWEEREQGSR,YLAGKPQQEH, IYIEQGNGITGM, TEVWDSNEQ	Orsini-Delgado et al. 2016
	Glutelin	HH, HL, LH, LHH	Silva-Sánchez et al. 2008
Anticancer	Amarantin (11S globulin)	VVV, GQ	Montoya-Rodríguez et al. 2015
Immunomodulatory	Total protein (hydrolysates)	SSEDIKE	Moronta et al. 2016a; Moronta et al. 2016b
	Glutelin	EAE, GFL, KRP, TKPR, YG, YGG	Silva-Sánchez et al. 2008

(*continued on next page*)

Table 5. (*Continued*).

Bioactive function	Protein source	Bioactive Peptide/Peptide sequence	Reference
Hypocholesterolemic	Total protein (hydrolysates)	GGV, IVG, VGVL	Soares et al. 2015
Antimicrobial	Total protein	VGECVRGRCPSGMCCSQFGYCGKGPKYCG (*Ac*-AMP1) VGECVRGRCPSGMCCSQFGYCGKGPKYCGR (*Ac*-AMP2)	Broekaert et al. 1992
	Total Protein	AGECVQGRCPSGMCCSQFGYCGRGPKYCGR (*Ar-AMP*)	Lipkin et al. 2005
	Total protein	CPSGMCCSQFGYCGK (*Ay*AMP)	Rivillas-Acevedo and Soriano-García 2007a; Rivillas-Acevedo and Soriano-García 2007b
	Albumin	KK	Montoya-Rodríguez et al. 2015
Antidiabetic	Total protein (hydrolysates)	AP, GP, FP, GP	Montoya-Rodríguez et al. 2014
	Albumin	MA, LP, LL, LA, FA, VA, FP	Montoya-Rodríguez et al. 2015
	Amarantin (11S globulin)	HA, MA, LL, LP, AP, FA, MP, PA, VA, FP, LA, PP, KA, VV, VP,	Montoya-Rodríguez et al. 2015
	Glutelin	AP, FA, FP, GP, GPR, GQ, HA, IPI, KA,LA, LL, LP, MA, MP, PA, PP, PPLP,PPPA, VA, VP, VPL, VV	Silva-Sánchez et al. 2008

See Table 2 for the amino acid nomenclature used in this table.

concentrated presented a reduction of serum LDL protein and triglycerides compared to control group; the liver also showed a reduction of total cholesterol and triglycerides, and the fatty acid synthase decreased in its activity. Mendonça et al. (2009) showed that hamster fed with amaranth protein isolates reduced total plasma cholesterol and non-HDL-cholesterol levels. Soares et al. (2015) identified peptides with HMG-CoA enzyme activity, a key enzyme in the biosynthesis of cholesterol. They reported GGV, IVG, and VGVL peptides inhibiting the activity of HMG-Co reductase, suggesting a possible hypocholesterolemic effect.

The physiological effect of the antioxidant peptides form amaranth seed proteins has been proved in different studies (Guzmán-Maldonado and Paredes-López 1998). Silva-Sánchez et al. (2008) reported the antioxidant potential of four peptides rich in histidine encrypted in the amaranth 11S globulin. Tironi and Añón (2010) found peptides with high antioxidant capacity from *A. manteggazianus* in all protein fractions. (Orsini-Delgado, Tironi, and Añón 2011) probed *in vitro* the antioxidant effect of amaranth peptides derived from multi-enzymatic peptidases. Later on, the same group investigated the antioxidant potential of peptides released by gastrointestinal digestion and identified a high increment in the scavenging activity against different radicals, such as peroxyl, hydroxyl and peroxynitrites (Orsini-Delgado et al. 2015). Also, Sabbione et al. (2016) obtained antioxidant peptides derived from the activation of endogenous amaranth proteases, and they found more antioxidant activity by the hydrolysates than the protein isolate from the amaranth seed flour. Many studies have reported the benefits of the peptides derived from amaranth proteins; however, amaranth hydrolysates provide a complex combination of peptides with different physical properties (Le Maux, Nongonierma, and Fitzgerald 2015).

In the last years, bioinformatics and protein sequencing have simplified the analysis of the effect of peptides and facilitated subsequent experimentation (Moruz and Käll 2016). In this sense, Montoya-Rodríguez et al. (2014) characterized antioxidant peptides from amaranth hydrolysates, and identified different antioxidant amino acids, such as lysine, proline, histidine, glycine and threonine. In Montoya-Rodríguez et al. 2015 determined, by bioinformatic studies, that the amaranth 11S globulin encrypted diverse di- and tripeptides with antioxidant activities. Besides, Orsini-Delgado et al. (2016) identified four peptides from the acidic subunit of the 11S globulin with high antioxidant capacities.

Amaranth contains proteins and peptides with anti-tumoral and anti-proliferative effects (Martínez-Cruz, Cabrera-Chávez, and Paredes-López 2014). For example, Yu et al. (2001) isolated a lectin from *A. mantegazzianus* and concluded that amaranth lectin can have a marked effect on the inhibition of malignant cancer cells. Barrio and Añon (2010) worked with *A. mantegazzianus* protein hydrolysate and found that it produced morphological changes and caused a rearrangement of the cytoskeleton in UMR106 cell line, inhibited cell adhesion and induced apoptosis and necrosis. Lunasin is also a promising peptide involved in prevention of different types of cancers. Lunasin was discovered in soybean and then was found in amaranth (Hernandez-Ledesma, Hsieh, and Ben 2009b; Hsieh, Hernández-Ledesma, and De Lumen 2010). Maldonado-Cervantes et al. (2010) reported that amaranth lunasin is a highly efficient peptide to prevent cancer, mainly because it is capable of enter into the nucleus of the cell and inhibits the transformation of NIH-3T3 spotlights cancerous cells.

Peptides from extruded amaranth inhibited inflammatory process in human and mouse macrophages by preventing the inactivation of NF-ƙB signaling (Montoya-Rodríguez et al. 2014). Similarly, Moronta et al. (2016a) determined that amaranth protein hydrolysates have immunomodulatory effects on epithelial cells through the NF-ƙB signaling pathways;also, they identified the peptide SSEDIKE, which has the ability to attenuate the activation of ephitelial cells. The same authors reported that SSEDIKE peptide inhibits the allergic reaction in mice with food allergy, prevents IgE secretion, and intestinal inflammation control preventing the activation of NF-ƙB (Moronta et al. 2016b).

Peptides with antimicrobial effect in the plasma membrane of microorganism are found in amaranth grains (Broekaert et al. 1997). Broekaert et al. (1992) isolated two antimicrobial peptides (*Ac*-AMP1 and *Ac*-AMP2) from *A. caudatus*, which bind to chitin in an irreversible way and inhibit the growth of different plant pathogenic fungi and show some activities against Gram-positive bacteria. The antimicrobial peptide Ar-AMP was isolated from *A. retroflexus* seeds, its sequence belongs to the hevein-like family of antimicrobial peptides with six cysteine residues; also, this peptide effectively inhibited the growth of different fungi (Lipkin et al. 2005). An antifungal peptide *Ay*-AMP was isolated from *A. hypochondriacus* seeds which has the capacity to inhibit the growth of *Candida albicans, Trichoderma* sp., *Fusarium solani, Penicillium chrysogenum, Geotrichum candidum, Aspergillus candidus, Aspergillus schraceus*, and *Alternaria alternata* (Rivillas-Acevedo and Soriano-García 2007a; Rivillas-Acevedo and Soriano-García 2007b). In addition, Pribylova et al. (2008) identified that the gene AMP2 in *A. caudatus, A. albus, A. cruentus, A. blitum, A. hybridus, A. hypochondriacus, A. retroflexus* and *A. tricolor*.

Amaranth peptides have the potential to diminish some key enzymes associated to type 2 diabetes, such as α-amilase and DPPIV. Conforti et al. (2005) reported the *in vitro* inhibition of α-amilase from two amaranth varieties that involve the digestion of starch and reduction of glucose absorption; however, they did not find if this effect was caused by peptides. (Velarde-Salcedo et al. 2013) reported the inhibitory effect against DPPIV enzyme by different peptides encrypted in amaranth globulin and glutelin. These amaranth peptides could be used as a novel therapy to prevent and diabetes treatment.

5.3. Genetic engineering to improve the functional properties of peptides

Amaranth protein globulin 11S or amarantin contained an array in their amino acid sequences of different potential bioactive peptides that confer important health benefits such as ACE, DPPIV and antioxidant inhibition effects (Montoya-Rodríguez et al. 2015). Amarantin gene is an excellent candidate to be expressed in diverse crops to improve their nutritional value as staple foods with a higher amount of bioactive peptides with different functional activities. Since the middle of 90′s, this protein was subjected to different molecular studies to

understand its processing and deposition in the amaranth grain (Barba De La Rosa et al. 1996). The importance of amaranth globulin 11S has led researchers in the last few decades to isolate, modify, overexpressed and purified amarantin gene and protein in *E. coli* cells. In this context, Osuna-Castro et al. (2000) overexpressed amarantin in *E. coli* and after purification found *in vitro* a proper refolding of this protein; in addition, the protein expressed and purified from *E. coli*, exhibited the same properties than the native amarantin from the seed (Barba se La Rosa et al. 1996). (Medina-Godoy et al. 2004) improved the potency of purification of the amarantin. They cloned and expressed a modified cDNA of histidine-tagged 11S globulin from *A. hypocondriacus* in *E. coli* bacteria; the resulting amarantin expressed was purified in one step with high yields. Amarantin protein is susceptible to be modified in its acidic subunit with the potential as a functional and nutraceutical molecule. This subunit contains four hypervariable regions of five regions detected in the 11S seed globulin (Tandang-Silvas et al. 2012). In that sense, Luna-Suárez et al. (2008) modified the third variable region of the acidic subunit of a His-tagged 11S amarantin and expressed in *E. coli*. The hydrolyzed and modified amarantin, showed a higher inhibitory activity against ACE than the native seed amarantin (Luna-Suárez et al. 2010). Similarly, (Arano-Varela, Dominguez-Dominguez, and Paredes-López 2012) expressed amarantin and evaluated different parameters in a bioreactor to obtain a high concentration of the recombinant acidic subunit, and demonstrated that the aeration rate and temperature were the most important variable to increase the protein yield. (Castro-Martínez, Luna-Suárez, and Paredes-López 2012) increased in a reactor around three-fold the protein yield expressed as a modified amarantin using different parameters such as temperature, agitation speed, and oxygen conditions.

Later, (Morales-Camacho, Dominguez-Dominguez, and Paredes-López 2013) expressed the acidic subunit of the amarantin manipulating parameters in a bioareactor when they used two minimal media supplemented with the inducer isopropyl-β-D-thioglactopyranoside or lactose, and found a high yield of the recombinant acidic subunit in a short time of induction. Similarly, Morales-Camacho et al. (2016) modified the C-terminal in the fourth variable region of acidic subunit of amarantin by inserting four VY antihypertensive peptides and expressed in *E. coli*. They found that modification of the variable region improves the thermal stability of amarantin acidic subunit. Another system was used to modified and expressed amarantin gene. In this context Medina-Godoy et al. (2006) used *Pichia pastoris* to insert a peptide that was tagged to retrieve the amarantin and overexpress and enhance the protein.

Amarantin gen is a candidate to be expressed in different important crops in order to improve the bioactive peptides and nutritional value of staple foods. Valdez-Ortiz et al. (2005) cloned the amarantin gene and transformed tobacco plants; they found that the protein retrieved its biochemical and physiological properties of the native amarantin. Rascón-Cruz et al. (2004) isolated and used the 11S globulin cDNA to transform maize plants; they analyzed and evaluated the insertion and expression of the amarantin gene in transformed plants. When the amarantin was accumulated in the maize seed, their content of essential amino acids profile such as Lys and Trp increased in relatives non-transformed plants. Similarly, Germán-Báez et al. (2014) used acidic subunit of amarantin from *A. hypocondriacus* and transformed tomato fruits; they found an increase of total protein content and higher concentrations of essential amino acids such as Val, Tyr, Ile and Leu. By the way, albumin gene that coded an important protein in amaranth, was used to transform potato tuber plants with the aim of improving nutritional quality of tuber proteins; the introduction of this gene imparted an increase in total protein and in essential amino acids as well as in phytoesterols (Chakraborty, Chakraborty, and Datta 2000; Shekhar et al. 2016).

6. Chia

Chia (*Salvia hispanica* L.) is native to Central Mexico up to Northern Guatemala, and its use as a food source has been dated as far back as 3,500 BC. The Salvia genus is the largest of the Lamiaceae family, with nearly 1000 species scrubs. The word "Chia" is derivate from Nahuatl (Mexican indigenous language) and it means oily. It is an annual plant that grows around 1 m and has oppositely arranged leaves with small white and purple hermaphrodite flowers. This plant was cultivated for its taste and was also used in folk medicine. Later, between 1500 and 900 BC Aztecs, Mayas and Incas used the seeds to prepare medicine, foods and paintings. In pre-Columbian cultures, it was the main staple crop after beans and maize, and was an integral part of diet of these civilizations, providing to these civilization important compounds that made their diet even superior to today's one. In addition, chia seeds are also a source of energy and are promoted as health food product (Ayerza, 2009). Nowadays the plant is considered as the superfood due of the 21st century to its nutraceutical potential (Capitani et al. 2012; Jamboonsri et al. 2012; Muñoz et al. 2013; Ullah et al. 2015; Orona-Tamayo, Valverde, and Paredes-López 2017b).

People has increased recently the consumption of chia due to its health benefits properties and nutritional value. It can now be found at markets in different brands and preparations like raw seeds, flour, food supplement, oil capsules, in yoghurts, drinks, energy bars, cereal, peanut butter and bakery products, and also animal feed formulations; mainly for horses, birds and rabbits. Raw chia seeds and seed flour are becoming popular and they may be added to muesli, breakfast cereals and fruit, nut and different seed mixes, shakes, desserts or homemade bakery products (Reyes-Caudillo, Tecante, and Valdivia-López 2008; Peperkamp 2014; Valdivia-López and Tecante 2015; Orona-Tamayo, Valverde, and Paredes-López 2017b).

6.1. Nutritional composition

The nutritional content of chia seeds includes 25–40% fat, 15–24% protein, and 26–41% carbohydrates and several minerals. The fat fraction has a high content of essential polyunsaturated fatty acids which comprise 55–64% linolenic acid ($\omega-3$) and 19–20% linoleic acid ($\omega-6$). $\omega-3$ fatty acids from chia (α-linolenic, eicosapentanoic and docosahexanoic acid) and $\omega-6$ (linoleic and arachidnonic acids) are essential polyunsaturated fatty acids (PUFAs). Other important nutritional aspects of the

seeds are the content of total dietetic fiber, 42% of total dry weight (Gómez-Favela et al. 2017), and the high-quality amino acids. Also, chia seeds contain high levels of phenolic compounds with important antioxidant capacity. The seeds contain gallic, caffeic, chlorogenic, ferulic and rosmarinic acids; other important phenols such as myricetin, quercetin, and kaempherol, as well as different isoflavones like daidzin, glycitin, genistin, glycitein, and genistein (Muñoz et al. 2013; Martínez-Cruz and Paredes-López 2014). The presence of these nutraceutical components and the healthier life style of the population have increased the popularity of this plant, and led to main producers of chia such as Bolivia and Paraguay. Mexico, Argentina and Australia are emerging producer as a result of the increasing demand of this seed.

The protein content of chia seeds (15–24%) is higher than other cereals like maize (14%), wheat (14%), oats (15.3%), barley (9.2%) and rice (8.5%). Besides, it comprises high concentration of essential amino acids (histidine, isoleucine, methionine, phenylalanine, threonine and tryptophan) and is an excellent source of sulfur amino acids (cysteine and methionine) as well as arginine, aspartic and glutamic acids. Globulins are the major protein fraction which constitute around 55% of the total storage proteins, followed by 18% albumins, 15% glutelin and 12% prolamin (Sandoval-Oliveros and Paredes-López 2013; Orona-Tamayo et al. 2015; Gómez-Favela et al. 2017; Orona-Tamayo, Valverde, and Paredes-López 2017b).

6.2. Bioactive peptides

The high amount of proteins in chia encrypts in their sequences biologically active peptides with different nutraceutical properties, including antihypertensive, antioxidant, antidiabetic and other important functions (Figure 1). Salazar-Vega et al. (2012) and Segura-Campos et al. (2013b) showed that peptides obtained from extensive hydrolysis inhibited more efficiently ACE activity than peptides from shorter hydrolysis. Segura-Campos et al. (2013a) reported that peptides from the globulin fraction, subjected to an extensive enzymatic hydrolysis, had high ACE-inhibitory activity and this was increased in peptides with low-molecular weight (<1 kDa; 69.3% of ACE-inhibition). Recently, Orona-Tamayo et al. (2015) found that peptides from albumin and globulin fractions exert more inhibition effect against ACE-enzyme than peptides from the other proteins fractions, similar results were found by Segura-Campos et al. (2011). The biological activity of chia proteins hydrolysates with ACE inhibition is related to the amino acid sequence of the peptides encrypted in the storage proteins, and the activity is influenced by the C-terminal. Chia seeds contain a high concentration of hydrophobic amino acids that include proline, isoleucine and phenylalanine, which have high ACE-inhibitory activity (Murray and FitzGerald 2007; Alemán et al. 2011a; Segura-Campos et al. 2013a; Orona-Tamayo, Valverde, and Paredes-López 2017b). Therefore, peptides with ACE-inhibitory activity from chia seeds could be a natural treatment for hypertensive patients. Diabetic individuals with cardiovascular risk, supplemented with 37 g/day of ground chia seeds, showed reduction in systolic blood pressure (6.3 mm Hg) compared to control patients (Vuksan et al. 2007). However, Nieman et al. (2009) evaluated the hypertensive effect of 50 g/day of whole or ground chia for 12 weeks and no differences in blood pressure were found. The same authors supplemented overweight women with 25 g/day of whole or ground chia for 10 weeks

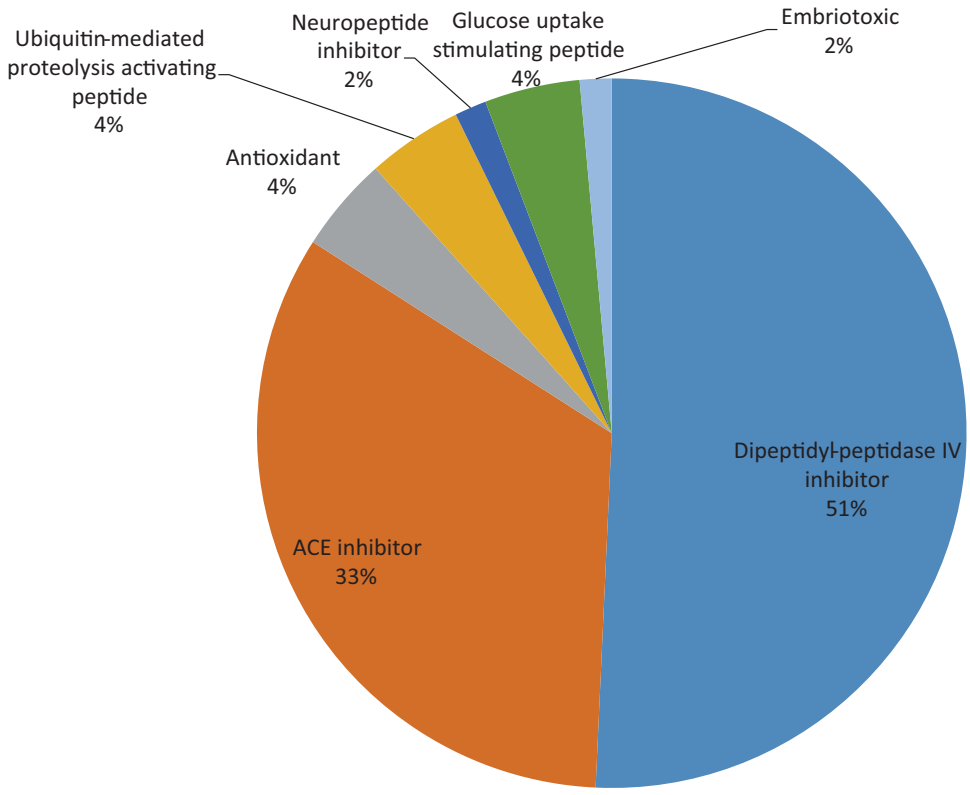

Figure 1. Bioactive peptides from chia (*Salvia hispanica*) globulin fraction.

and reported that the ingestion of chia did not influence cardiovascular risk factors (Nieman et al. 2012). On the other hand, Toscano et al. (2014) evaluated, in under treatment and non-treatment hypertensive patients, the incorporation of 35 g/day of chia seed flour into their diet for 12 weeks, and found a reduction of blood pressure (5.2 mm Hg) in treated patients, while the control group showed no change, concluding that chia consumption is able to decrease the blood pressure in hypertensive patients.

Orona-Tamayo et al. (2015) showed that peptides from albumin and globulin fractions presented high antioxidant capacity against DPPH and ABTS with lower IC_{50}, and peptides from glutelin and prolamin fractions showed lower antiradical activity against these oxidants. They concluded that albumin and globulins encrypted important peptides with a high antioxidant capacity. These authors determined that peptides from prolamin showed a higher capacity to chelate Fe^{+2} ion than peptides from globulin and glutelin fractions. In living systems, the presence of transient metal ion, such as Fe^{2+} and Cu^{2+} involve the formation of ROS (Canabady-Rochelle et al. 2018). These results indicate that peptides from globulin and prolamin are the most powerful chelating components in chia seeds.

6.3. Genetic engineering to improve the functional properties of peptides

Nowadays genetic, molecular biology and genomic information on bioactive peptides from chia is missing, therefore there is an opportunity to use different mutagenesis and other advanced molecular tools to facilitate rapid genetic improvement of proteins and peptides in this plant. In that sense, Jamboonsri et al. (2012) chemically mutagenized chia seeds with ethyl methanosulfonate to obtain seeds that generated chia early flowering lines able to flower under a short photoperiod; under field conditions these lines flowered at a photoperiod of around 14 h, and the plants produce seeds in a range of environments in temperate areas.

New generation tools can help us to reveal different gene function related to important metabolic networks. The high polyunsaturated fatty acids content in chia seeds makes this crop very attractive as food and for different industrial uses. From a commercial point view, it is desirable that seeds contain high levels of triacylglycerols enriched with beneficial fatty acids (Brown et al. 2012). Different researches have focused their attention the identification of genes that encoding enzymes related to fatty acids and triacylglycerol biosynthesis (Ruiz-Lopez et al. 2015). In this context, Xue et al. (2017) isolated from RACE method two full-lengh Fatty Acid Desaturases (*ShFAD2–1* and *ShFAD2–2*) genes that encoded key enzymes for linoleic acid and α-linolenic acid biosynthesis in Chia. Both ShFAD2-1 and ShFAD2-2 proteins possess strong transmembrane helices, three histidine motifs and a C-terminal ER-located signal, and their heterologous expression in *Saccharomyces cerevisiae* indicated that both genes encoded a biofunctional delta-12 oleate desaturase. *ShFAD2-2* was mainly expressed in flowers and early-stage seeds while *ShFAD2*-1 expression was almost constitutive in different organs. This study can provide insights into molecular mechanism of high α-Linolenic acid (ALA) traits of *S. hispanica*. Sreedhar et al. (2015) analyzed a global transcriptome in chia seed development, and found genes involved in the lipid metabolism and oil accumulation in chia seeds. However, chia is a diploid plant with only 12 chromosomes (Estilai, Hashemi, and Truman 1990), which facilitates rapid genetic improvement and the plant breeding (Araki and Ishii 2015) by new molecular generation technologies. This genomic information may be useful to improve the quality and quantity of proteins, peptides and oil from chia seeds.

7. Quinoa

Quinoa (*Chenopodium quinoa*) is a flowering plant from the Amaranthaceae family. It was cultivated 7,000 years ago by the Incas in the Titicaca Lake and then was spread to Ecuador and Chile. Actually it is mainly cultivated in Bolivia, Chile, Peru, Ecuador, and Colombia; as well as in few other countries such as England, Sweden, Denmark, the Netherlands, Italy, Kenya and France (Bhargava, Shukla, and Ohri 2006; Bhargava, Shukla, and Ohri 2007; Fuentes et al. 2009; Iqbal 2015).

Quinoa has large genetic variability and great capacity to adapt to different agro-ecological edaphic conditions. It shows tolerance to frost, salinity and drought; also has the potential to grow on marginal soils, it may also be tolerant to disease, pests, and it can grow at pH between 4.8 and 9.5. Five ecotypes have been identified: *salares* (salt flats), highlands, inter-Andean valleys, *yungas* and coastal-lowlands (Jacobsen, Mujica, and Jensen 2003; Repo-Carrasco, Espinoza, and Jacobsen 2003; Iqbal 2015; Aloisi et al. 2016; Rizzello et al. 2017).

This grain is considered an excellent functional food. It is part of FAO strategy to encourage the cultivation of traditional crops as means of contributing to food security for the 21st century; and it is considered by NASA as an emerging crop with excellent nutritional properties, mainly due to its protein and unique amino acid composition. Regarding economics and sustainability, sweet quinoa varieties are the most promising because they provide more high-quality protein than the bitter crops. It is considered a pseudocereal and the whole grain may be used to fermented to produce beer, or in bread, soups, biscuits, drinks, etc.; also, the whole plant is used as green forage to feed cattle, pigs and poultry (Schlick and Bubenheim 1993; Jacobsen, Mujica, and Jensen 2003; Jancurová, Minarovicová, and Dandar 2009; Vega-Gálvez et al. 2010; Iqbal 2015).

7.1. Nutritional composition

The nutritional composition of quinoa varies among ecotypes due to genetic variability and environmental conditions (Repo-Carrasco, Espinoza, and Jacobsen 2003). Its protein content (13.8 to 16.5%) is higher than barley (11.0%), rice (8.8%), maize (10.5%), rye (11.6%) and sorghum (12.4%); but, the importance relies on the high level of essential amino acids, which is also higher than common cereals. Quinoa has a well–balanced amino acid profile with high amounts of lysine and methionine; it contains 1.4 times more lysine than soybean, twice more than maize, 2.3 more than wheat. Its proteins do not contain gluten, which is a promising characteristic for celiac patients (Koziol 1992; Aubrecht and Biacs 2001; Mujica-Sanchez et al. 2001; Drzewiecki et al. 2003; Comai et al. 2007; Alves, Rocha, and

Gomes 2008; James 2009; Jancurová, Minarovicová, and Dandar 2009; Vega−Gálvez et al. 2010; Stikic et al. 2012; Escuredo et al. 2014). Storage proteins of quinoa are mainly albumins (2S) and globulins (11S) (35 and 37%, respectively); among the 11S, globulins A and B are the most abundant fractions, and their amino acidic sequence was almost identical (Brinegar and Goundan 1993; Brinegar, Sine, and Nwokocha 1996; Gorinstein et al. 2002; Wright et al. 2002; Watanabe et al. 2003; Gorinstein et al. 2005; Capriotti et al. 2015). On the other hand, Aloisi et al. (2016) determined that salinity altered the seed proteome and amino acid profiles, which, increasing the concentration of bioactive molecules and oxidant activity of protein extracts.

Quinoa contains important levels of vitamins (A, B2, E) and minerals (Ca, Fe, Cu, Mg, Zn); lipids between 2.0 to 9.5% are rich in linoleic (49 to 56%) and α-linolenic (9 t o12%) acids, which correspond to 88% approximated of the total fatty acids (Koziot 1990; Koziol 1992; Ando et al. 2002; Repo-Carrasco, Espinoza, and Jacobsen 2003; Ryan et al. 2007; Borges et al. 2010).

The seeds also comprise important bioactive compounds, such as vitamin B2 and E, carotene, tocopherols and phenolic compounds. It is good source of flavonoids, quercetin and kaempferol glycosides. Phenolic compounds, vitamins, proteins and fat may vary between quinoa ecotypes; which are related to the environmental conditions, farming techniques and genetic factors; antioxidant and antimicrobial activities also vary among genotypes and environment (Repo-Carrasco, Espinoza, and Jacobsen 2003; Nsimba, Kikuzaki, and Konishi 2008; Alvarez-Jubete et al. 2010b; Miranda et al. 2011; Miranda et al. 2013; Miranda et al. 2014; Iqbal 2015).

7.2. Bioactive peptides

There is scarce information reported in literature about bioactive peptides of quinoa proteins. That is why it is necessary to carry out more studies to demonstrate the nutraceutical potential of the proteins of this pseudocereal.

Fortunately, Rizzello et al. (2017) reported that five bioactive peptides from quinoa (5 to 9 amino acid residues) contain important antioxidant activity. They were found in the NCBInr database as encrypted in different quinoa proteins. IVLVQEG and TLFRPEN are encrypted in a quinoa globulin B. VGFGI and FTLIIN released from salt sensitive protein, and LENSGDKKY encrypted in a maturase K protein.

Genetic engineering to improve the functional properties of peptides

As indicated before, there is almost no information based on genetic engineering of this important seed. Fortunately, very recently Zou et al. (2017) sequenced a genome of stress tolerance of quinoa and found that it is associated with the expansion of genes involved in ion and nutrient transport, abscisic acid (ABA) homeostasis and signaling, and enhancing basal-level ABA response. Also, Jarvis et al. (2017) sequenced a chromosome-scale reference genome for quinoa which facilitated the identification of the transcription factor likely to control the production of anti-nutritional triterpenoid saponins found in this crop.

8. Safety of bioactive peptides from seed

Seeds contain high concentration of storage proteins with important levels of different amino acids, which have diverse functional biopeptides. There is plenty information on the benefits of seeds peptides; moreover, the research has emphasized the peptides efficacy, and now it is necessary to analyze their safety, allergenicity and potential toxicity (Aluko and Monu 2003; Yamamoto, Ejiri, and Mizuno 2003; Luna-Vital et al. 2015; Montoya-Rodríguez et al. 2015; Nongonierma et al. 2015; Orona-Tamayo et al. 2015; Valverde et al. 2016; Orona-Tamayo and Paredes-López 2017a; Orona-Tamayo, Valverde, and Paredes-López 2017b).

Toxic sequences of peptide contain high concentrations of proline, histidine and asparagine, as well as cysteine residues. These peptides contain dominant amino acids such as valine, arginine, threonine, glutamine, methionine, leucine, lysine, isoleucine, phenylalanine, and alanine. Peptides with ACE, renin and DPPIV inhibitory effects, contain residues of phenylalanine, leucine, arginine, tryptophan, isoleucine and high concentration of proline residues which suggests that these peptides can be potentially toxic (Gupta et al. 2013; Lafarga and Hayes 2017).

Gupta et al. (2013) developed*in silico* models to predict toxicity of peptides and proteins, named as "ToxinPred" (http://www.imtech.res.in/raghava/toxinpred/). They use various properties of the peptides to predict toxicity, minimal mutations in peptides to increase or decrease toxicity, and toxic regions of proteins. It is worth to mention that the safety of the bioactive peptides, and their hydrolysates used as food ingredients for therapeutic proposes, should be also evaluated *in vitro* and *in vivo*. However, no side effects have been reported in consumers using bioactive peptides from food.

9. Conclusions

Nutraceuticals or functional foods are any product derived from food source with extra health benefits, in addition to the basic value of the food. They may be considered non-specific biological therapies used to promote general well-being, control symptoms and prevent malignant process. In recent years, the relationship between diet and health has been more clear; however, it was known since the time of Hippocrates, who said "let your food be your medicine". Moreover, further clinical human studies should be conducted to verify the health benefits of bioactive peptides. The increase rate in the advancement proteomics, bioinformatics, peptide libraries, and modification strategies, will support the use of bioactive peptides as novel drugs in future clinical applications.

On the other hand, the development of healthier foods with bioactive peptides is a great scientific and technological challenge. Nowadays, it is possible to find them in the market, especially in countries like Japan. These products are accepted because peptides possess favorable pharmacokinetic profiles, tissue distribution patterns, rapid clearance from the blood, non-target tissues, low toxicity, immunogenicity and good solubility properties.

Some techniques have been widely used to improve the nutritional quality of the protein of maize, common bean,

amaranth, chia and quinoa; however, only in amaranth has tried to raise the profile of the bioactive peptides, but, indirectly have increased in each case that became transformation with the gene that encodes for any of the mentioned seed storage protein.

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