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The Use of UniProtKB/BIOPEP for the Analysis of Oat Globulin Physicochemical Parameters and Bioactivity

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Abstract

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The physico-chemical properties of oat proteins (globulins) were determined and an analysis was done whether products of *in silico* proteolysis contain mono- and multi-functional peptides with various biological activity. The MW(s), calculated by the ProtParam program, for precursors of 12S and 11S globulins and proteins without signal peptides were in the range of 50.78–61.86 kDa. The pH at which the solubility of the proteins under analysis was the lowest ranged from 7.29 to 9.44. A simulation of proteolysis with three enzymes (pepsin, trypsin, and chymotrypsin A) in the optimum conditions of the enzyme action can produce 6–8 bi-functional, 5–10 mono-functional biopeptides from oat globulins (12S, 11S globulins), and one tri-functional biopeptide (VY). The mono-functional biopeptides exhibited the activity of DPPIV inhibitors or ACE inhibitors, and the multi-functional biopeptides can exhibit the activity of inhibitors of both enzymes (DPPIV and ACE). Sensory peptides accounted for 43% of all the released mono- and multi-functional biopeptides.

Keywords: *in silico* proteolysis; multifunctional biopeptides; oat storage proteins; protein database

Abbreviations: accession number (AC); angiotensin-I-converting-enzyme (ACE); antioxidative peptide (AOXp); caodulin-dependent phosphodiesterase 1 (CaMPDE); database of proteins and bioactive peptides (BIOPEP); dipeptidyl peptidase IV (DPPIV); Expert Protein Analysis System (ExPASy); glucagon-like peptide-1 (GLP-1); glucose-dependent insulinotropic polypeptide (GIP); glucose uptake stimulating peptide (GUSp); identification number (ID); isoelectric point (pI); molecular weight (MW); two-dimensional electrophoresis (2-DE); Universal Protein Resource Knowledgebase (UniProtKB)

Amino acid sequences are necessary in studies of protein/peptide structures and the physicochemical and biological properties of these compounds are applied in proteomic studies to identify proteins/peptides separated, for example, by the 2-DE technique (Lafarga *et al.* 2014; Szerszunowicz *et al.* 2017). UniProtKB (http://www.uniprot.org/uniprot/) is one of the largest databases of amino acid sequences of proteins and their fragments (written with one-letter amino acid codes) of various origins (Magrane & the UniProt Consortium 2011; Pundir *et al.* 2015). UniProtKB is a database of the UniProt datasets, the largest, most comprehensive catalogue of information on proteins, including their taxonomy, functions and post-translation modification. The UniProtKB is accessible through the UniProt website (http://www.uniprot.org) (Jain *et al.* 2009; Pundir *et al.* 2015); it is also part of the resources of the global bioinformatics portal ExPASy (http://www.expasy.org), which also provides access to popular bioinformatics programs, such as ProtParam, ProtScale, Compute pI/MW, PeptideMass, PeptideCutter (Gasteiger *et al.* 2005).

Each protein can be a source of biologically active peptides (biopeptides), which are protein fragments that can become bioactive after being released from their parent proteins by proteolytic enzymes. Such biopeptides are formed by proteolysis of proteins produced by digestive enzymes in the human alimentary tract; they can also be formed during the technological processes in food production (Möller *et al.* 2008; Bhat *et al.* 2015). This fact was the basis for creating BIOPEP (http://www.uwm.edu.pl/bio-

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chemia or http://www.omictools.com/biopep-tool) (Minkiewicz *et al.* 2008). Using the amino acid sequences and the necessary tools in the BIOPEP database, users can carry out *in silico* proteolysis and identify products which can be potentially released, including biopeptides. Biopeptides can have a beneficial effect on the function of the circulatory system in mammals (antihypertensive and anticoagulant peptides), regulate the level of glucose and eliminate free oxygen radicals during oxidative stress (Möller *et al.* 2008; Morato *et al.* 2013; Bhat *et al.* 2015).

This study used oat globulins due to their dominating presence in grain (they account for 50–80% of total protein), as well as to the beneficial amino acid composition of the proteins and lower content of prolamins (4–15% of total protein), regarded as coeliac-toxic (Klose & Arendt 2012).

The aim of the study was to determine selected physicochemical properties of oat storage proteins (globulins) and to analyse whether products of *in silico* proteolysis include mono- and multi-function peptides of various biological activities.

MATERIAL AND METHODS

From among the 290 of amino acid sequences of oat (*Avena sativa* L.) proteins and their fragments available in UniProtKB (accessed in November 2016), only six were those of globulins. Sequences of precursor proteins and those from which 24-amino acid signal peptides were removed before the analysis were used in the study.

Selected physicochemical properties of oat globulins. Using available sequences and the ProtParam program (including Compute pI/MW) in UniProtKB (http://web.expasy.org/cgi-bin/protparam/protparam), MW(s), pI(s) of the proteins were calculated, as well as the percentage (%) of each amino acid in each monomeric protein (Figure 1).

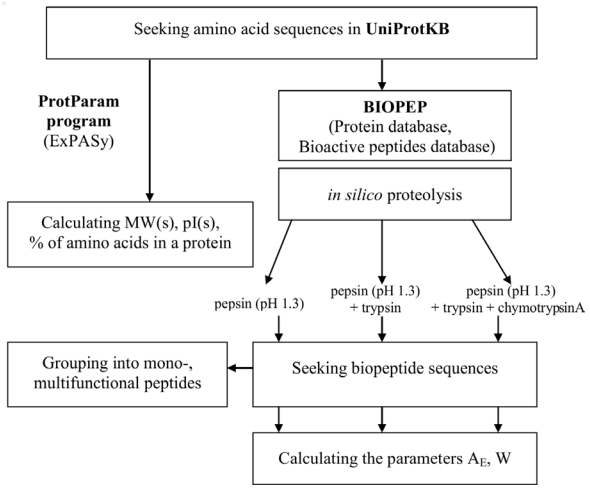

Figure 1. The procedure scheme

In silico hydrolysis of oat globulins with selected enzymes (BIOPEP). *In silico* proteolysis of 12 globulins (six complete proteins and the same number of proteins from which signal peptides were removed) was carried out with the 'Enzyme(s) action' application. This application is available by opening the 'analysis' panel, visible upon entering one of the databases of BIOPEP, e.g. Bioactive peptides database (Figure 1). An amino acid sequence, copied from UniProtKB, was entered in an empty window accessible after opening the 'for your sequence' tab. In order to perform the proteolysis of oat proteins, from among the 32 proteolytic enzymes available in the BIOPEP dataset, pepsin (pH 1.3) (EC 3.4.23.1) was used, followed by pepsin and trypsin (EC 3.4.21.4), and a system in which the specificity of the action of three enzymes was used (pepsin, trypsin and chymotrypsin A; EC 3.4.21.1). In total, 36 simulations of *in silico* hydrolysis were performed, in which 12 globulin sequences and three different enzymatic sets were used.

Obtaining in silico mono- and multi-functional biopeptides. Information on the released biopeptides is available by opening the 'search for active fragments' tab. The information was used to group the biopeptides into mono- and multifunctional (bi-, tri- functional) biopeptides. Moreover, quantitative parameters of proteolysis were calculated, including the frequency of the release of fragments with a given activity by selected enzymes (A_E parameter) and the relative frequency of the release of fragments with a given activity by selected enzymes (W parameter) (Minkiewicz *et al.* 2011).

RESULTS AND DISCUSSION

Selected physicochemical properties of oat globulins. Figure 2 shows the theoretically calculated percentage of individual amino acids in the proteins under analysis. Residues of glutamine (11–13.4%) and of aliphatic neutral amino acids, such as leucine (7–9.1%), glycine (7.1–7.6%), alanine (6.1–7.1%), valine (5.8–6.5%), dominate in the primary structure of precursors of oat globulins. A similar content of some of the above-mentioned amino acids in oat samples, which came from husked and hulless oat grains grown in organic and conventional farming

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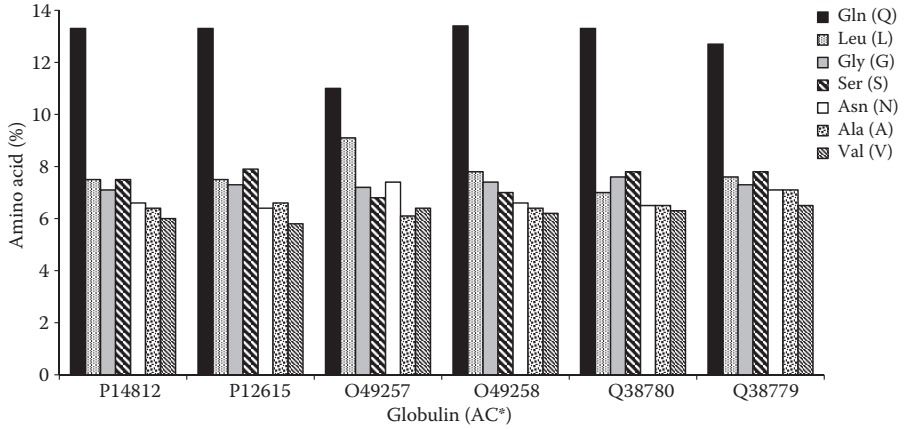

Figure 2. The content (%) of selected amino acids in the primary structures of globulins

The globulins were applied to precursor proteins; percentage of the amino acids calculated for complete protein sequences: R (5.6–6.6), E (4.4–5.6), P (4.4–4.9), F (5.8–6.0), I (4.9–6.1), T (3.7-4.3), and (D, C, H, K, M, Y) < 4%, including W < 1%; *accession number of the UniProtKB

systems, was confirmed by experimental research conducted by Vilmane *et al.* (2015). Oat samples were rich in essential amino acids such as leucine (7.77–11.98 g/kg), valine (5.29–8.17 g/kg) and phenylalanine (4.64–7.80 g/kg) (Vilmane *et al.* 2015).

Amino acid sequences of proteins/peptides deposited in the UniProtKB database and some bioinformatics programs made available through this base, e.g. the ProtParam program (Gasteiger *et al.* 2005), can be used in the research into different proteins to calculate the content of individual amino acids in protein monomers, pI(s) and MW(s). One of the examples of the use of the same bioinformatics tools as the ones used in this work was the research conducted by Lafarga *et al.* (2014). Lafarga *et al.* (2014), on the basis of amino acid sequences of meat proteins available in UniProtKB and the ProtParam program, calculated the concentration of selected amino acids, among other things branched-chain amino acids (isoleucine and leucine), aromatic amino acids (phenylalanine, tyrosine, and tryptophan) in meat proteins of porcine and bovine origin and in biopeptides obtained from these proteins.

Table 1 shows theoretical MW(s) of protein monomers and pH at which – since they are ampholytic compounds – their total charge is zero (isoelectric points). The MW(s) calculated for precursor proteins were in the range of 53.43–61.86 kDa. The pH values at which the solubility of the proteins was the lowest were in the range of 7.64–9.36. The MW(s) and pI(s) calculated for proteins without signal peptides were in the ranges of 50.78–59.12 and 7.29–9.44 kDa, respectively (Table 1). The parameters can be used in preliminary identification of oat proteins separated, for example, by the 2-DE technique, applied commonly in proteomic studies. This technique was used to separate prolamins of oats, and 13 spots (MW(s) range 27–34.6 kDa, pI(s) 5.7–7.6) were considered to be the most typical of this protein fraction, whereas the calculated (theoretical) numerical ranges of parameters for 41 sequences of avenins, gliadin-like avenins and their fragments were MW(s) 20.41–32.79 kDa and pI(s) 5.56–8.97 (Klose & Arendt 2012; Szerszunowicz *et al.* 2017).

Bioevaluation of oat globulin proteolysis products. Products obtained by *in silico* proteolysis of oat globulins were assessed for their bioactivity by comparing the obtained amino acid sequences with 3285 biopeptide sequences (44 activities, access November 2016), stored in BIOPEP (Bioactive Peptides Database). The database contains sequences of synthetic and experimental biopeptides, which, depending on the number of activities, have been entered two or more times and are saved under various, own ID(s). The amino acid sequences, ID, activity, as well as the position of a biopeptide in the protein sequence, were used in this study to group the obtained biopeptides into mono-, bi-, and tri-functional biopeptides (Table 1).

Hydrolysis of globulins only by pepsin can release biopeptides with the QF sequence, and NL biopeptides only from 12S globulins, and additionally YF biopeptides from 11S globulins (the latter were not released from a protein sequence without signal peptides). All the biopeptides released *in silico* were DPPIV inhibitors (Table 1). Lan *et al.* (2015) identified such peptides released from food proteins *in silico*

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Table 1. Selected physicochemical properties of oat globulins, and mono- and multifunctional (bi- and tri- functional) biopeptides obtained by *in silico* proteolysis with selected enzymes

No.	Protein name (accession number)			*In silico* hydrolysis**	
	parameters*			pepsin (pH 1.3), trypsin and chymotrypsin A	
	amino acid residues	molecular weight (kDa)	isoelectric point	type of peptide	sequences of biopeptides
1	12S seed storage globulin 2 (P14812)				
	518 (494)	58.68 (55.95)	7.64 (7.29)	mono	IF[2a], QK[2], AR[2], AL[1], DR[1], NL[1], PF[1], QF[1]; + QL[1b]
				bi	VF[1,2], SY[1,2a], GF[1,2], NF[1,2], TF[1,2], EF[3,4], IL[1,5]
				tri	VY[1,2,6]
2	12S seed storage globulin 1 (P12615)				
	518 (494)	58.54 (55.88)	8.78 (8.76)	mono	QK[2], AR[2], AL[1], DR[1], NL[1], PF[1], QF[1]; + QL[1b]
				bi	VF[1,2], GF[1,2], NF[1,2], TF[1,2], EF[3,4], IL[1,5]
				tri	VY[1,2,6]
3	12S globulin (O49257)				
	472 (448)	53.43 (50.78)	9.36 (9.44)	mono	QK[2], EAK[6], AL[1], DR[1], DR[1], NL[1], NL[1], QF[1], TL[1]; + QL[1b]
				bi	VF[1,2], GY[1,2], GF[1,2], SF[1,2], EF[3,4], IL[1,5]
				tri	VY[1,2,6]
4	12S globulin (O49258)				
	515 (491)	58.23 (55.58)	8.41 (8.49)	mono	QK[2], AL[1], DR[1], NL[1], NL[1], QF[1]; + QL[1b]
				bi	VF[1,2], GY[1,2], GY[1,2], SF[1,2], TF[1,2], EF[3,4], IL[1,5]
				tri	VY[1,2,6]
5	11S globulin (Q38780)				
	527 (503)	59.41 (56.66)	9.14 (9.20)	mono	QK[2], AL[1], DR[1], NL[1], QF[1]; + QL[1b]
				bi	VF[1,2], GF[1,2], GF[1,2], NF[1,2], TF[1,2], EF[3,4], VL[1,5], IL[1,5]
				tri	VY[1,2,6]
6	11S globulin (Q38779)				
	551 (527)	61.86 (59.12)	9.20 (9.26)	mono	GR[2], QK[2], QK[2], AL[1], DR[1], HR[1], NL[1], QF[1]; + QL[1b]
				bi	VF[1,2], GF[1,2], NF[1,2], TF[1,2], EF[3,4], VL[1,5], IL[1,5]
				tri	VY[1,2,6]

*ProtParam program; **BIOPEP database; the numbers in brackets concern globulins from which signal peptides were removed; the sequences of biopeptides released from precursor proteins and those without signal peptides (mature proteins) are the same; [a]not released from the mature protein (a protein sequence without signal peptide); [b]released from the mature proteins; [1]DPPIV inhibitor; [2]ACE inhibitor; [3]CaMPDE inhibitor; [4]renin inhibitor; [5]GUSp; [6]AOXp; some of the presented biopeptides are also sensory peptides, whose sequences are deposited in the Database of Sensory Peptides and Amino Acids. AR – salty taste enhancing peptide; IF, PF, GF, EF, VF, IL, VY, GY, YF, VL, GR – bitter peptides

and *in vitro*. DPPIV (EC 3.4.14.5) is an enzyme inactivating intestinal hormones (incretins), which increase postprandial insulin secretion by beta cells of pancreatic islets, decrease absorption of nutrients by slowing down the emptying of the stomach, and inhibit secretion of glucagon by alpha cells of pancreatic islets. Such incretins include: GLP-1 and GIP. DPPIV inhibitors are used in pharmacotherapy of type-2 diabetes (Nongonierma *et al.* 2013; Lan *et al.* 2015).

Pepsin hydrolysates obtained *in silico* from oat globulins contained one bifunctional TF biopeptide. This dipeptide inhibited the action of enzymes (DPPIV and ACE) (Nogata *et al.* 2009; Lan *et al.* 2015; Shamloo *et al.* 2015). ACE (EC 3.4.15.1) plays a key role in the regulation of blood pressure in mammals. It mainly affects the renin-angiotensin system, whose natural substrates include angiotensin I and bradykinin. ACE hydrolyses angiotensin I to angiotensin II and inactivates bradykinin, which results in a blood pressure increase. ACE inhibitors decrease blood pressure, which is why peptide inhibitors of ACE act similarly to many anti-hypertensive drugs

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(Nogata *et al.* 2009; Shamloo *et al.* 2015). The activities of a peptide enzyme inhibitors are differentiated by the IC_{50} value, defined as the concentration of the peptide (inhibitor), which reduces the enzyme activity by 50% (μM) in experimental conditions. The activity of peptides confirmed in experimental conditions is not always confirmed in *ex vivo* or *in vivo* (on animals) studies. The physiological effect of biopeptides is confirmed when intravenous or oral administration of such compounds to animals results in a decrease in systolic blood pressure in spontaneously hypertensive rats (Saito *et al* 1994; Möller *et al.* 2008; Shamloo *et al.* 2015). In order to confirm the physiological effect of peptide inhibitors DPPIV or the GUSp, the glucose level in blood or glycogen in animal livers are determined (Morato *et al.* 2013). Pepsin can release two bi-functional biopeptides TF (DPPIV, ACE inhibitors) and VL (DPPIV inhibitor and, at the same time, GUSp) from 11S globulins (Table 1). Nogata *et al.* (2009) identified a TF peptide with the ACE inhibitor activity (IC_{50} value 18 μM) among the products of wheat bran autolysis. TF and VL peptides have also been identified by other authors as DPPIV inhibitors (Lan *et al.* 2015).

The Bioactive Peptides Database contains values of IC_{50} for ACE inhibitors and for some DPPIV inhibitors, therefore the calculated A_E and W parameters are used in *in silico* proteolysis (Minkiewicz *et al.* 2011). A_E and W parameters calculated for the dominant activity (DPPIV inhibitors), for all the precursor proteins following hydrolysis with pepsin, were in the range of 0.0058–0.0085 and 0.0085–0.0126, respectively, and 0.0076–0.0112 and 0.0116–0.0165, calculated for the same sequences without signal peptides (mature proteins). The numerical quantity of the A_E parameter is the quotient of the number of peptides with a given activity (i.e. DPPIV inhibitors) released by a given enzyme (i.e. pepsin)/the number of amino acid residues in protein. The greater the number of the A_E parameter, the greater the number of peptides with a given activity (i.e. DPPIV inhibitor) is released in *in silico* conditions of the conducted process of hydrolysis by a specific proteolytic enzyme. However, the numerical value of the W parameter (the relative frequency of the release of fragments with a given activity by selected enzymes) is the quotient of the A_E parameter (the frequency of the release of fragments with a given activity by selected enzymes/the frequency of bioactive fragment occurrence in a protein sequence) (A parameter, this parameter takes the number of fragments with a given activity in a protein sequence as a dividend and the number of amino acid residues of protein as a divisor) (Minkiewicz *et al.* 2011). The values of A_E and W parameters calculated for the dominant activity (DPPIV inhibitors), for oat globulins from which 24 amino acid signal peptides were removed (a sequence targeting proteins to the secretory pathway or periplasmic space), and which were hydrolysed with pepsin are greater in comparison with the same parameters calculated for precursor proteins (with signal peptides). Decidedly more bioactive sequences (DPPIV inhibitors) were located outside the fragments of amino acid sequences defined as signal peptides. The gastric juice enzyme did not release any tri-functional biopeptide. The combination of the specificity of two enzymes (pepsin and trypsin) allows obtaining 3–6 bi-functional biopeptides from the analysed proteins.

The process of *in silico* digestion with three digestive enzymes (additionally chymotrypsin A) yields 6–8 bi-functional and 5–10 mono-functional biopeptides (Table 1). Hydrolysates of oat globulins contained mono-functional peptides, whose sequences were dominated by L or Q amino acids (Figure 2). Mono-functional biopeptides AL (IC_{50} value 882.13 mM) (Nongonierma *et al.* 2013), NL, QF were DPPIV inhibitors, whereas QK exhibited the activity of an ACE inhibitor (Table 1). Products of proteolysis included biopeptide DR and bi-functional biopeptides VF, GF, NF, TF (DPPIV and ACE inhibitors) and EF (CaMPDE and renin inhibitors). IC_{50} values for ACE inhibitors were 9.2, 630, 46.3 and 18 mM for VF, GF, NF, TF, respectively (http://www.uwm.edu.pl/biochemia/index.php/pl/biopep). Three dipeptides (EF, IR and KF) identified in the permeate obtained from ultrafiltration of pea protein hydrolysate exhibited weaker CaMPDE inhibiting properties, but they inhibited (IC_{50} values < 25 mM) ACE and renin strongly (Li & Aluko 2010). Enzymes such as ACE, renin (EC 3.4.23.15), and DPPIV play key roles in the control of hypertension and the development of type-2 diabetes and other diseases associated with metabolic syndrome (Lafarga *et al.* 2014). DPPIV inhibitors (drugs which increase the activity of natural GLP-1, e.g. sitagliptin, vildagliptin, and saxagliptin) and GLP-1 analogues (drugs which are substitutes of GLP-1) are effective antidiabetics, as they do not cause any weight gain, and are safe because of a minimum risk of the occurrence of hypoglycaemia (Fala & Writer 2015).

Zhang *et al.* (2015) studied the hypoglycaemic activity of oat hydrolysates prepared by proteolysis by alcalase (EC 3.4.21.62) on blood glucose concentration and insulin response in streptozotocin-induced diabetic mice. Streptozotocin is a compound which causes hypoinsulinaemia and hyperglycaemia and is used to

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generate diabetic animal models. Zhang *et al.* (2015) think that antidiabetic effects of oat hydrolysates can be caused by the presence of peptides with FLQPNLDEH and DLELQNNVFPH sequences. The authors think that the biological activity of these two peptides can be induced by two leucine residues and one phenylalanine residue present in their sequence. In this study, in the hydrolysates of oat globulins obtained as a result of *in silico* digestion with three enzymes (pepsin pH 1.3, trypsin, chymotrypsin A) there were NL and VF bioactive dipeptides (Table 1). NL biopeptide is a peptide inhibitor DPPIV, whose sequence is a fragment of the structure of FLQPNLDEH peptide, identified by Zhang *et al.* (2015). However, the VF dipeptide, classified as a bi-functional biopeptide – a peptide inhibitor DPPIV and ACE (Table 1), is located in the sequence of DLELQNNVFPH peptide (Zhang *et al.* 2015). Among the bi-functional dipeptides obtained from oat globulins in *in silico* conditions, dipeptides in structures with one phenylalanine residue (VF, GF, NF, TF, and EF) prevailed (Table 1). Bi-functional IL biopeptides can be released from all oat globulins, and VL biopeptide only from some. Both of these peptides are classified as DPPIV inhibitors and GUSp(s) (Table 1). Lan *et al.* (2015) determined the activity (IC_{50} value 74 mM) of the new VL peptide isolated from soy protein hydrolysates, and classified it as a strong DPPIV inhibitor. Studies have confirmed that di- and tri- peptides are actively and rapidly taken up by enterocytes via the intestinal oligopeptide transporter "Pept-1" (Morifuji *et al.* 2009). Dipeptides comprising branched-chain amino acids exhibited greater efficiency in translocating the glucose transporter type 4 to the plasma membrane and greater glucose uptake by animal skeletal muscle (Morato *et al.* 2013).

One tri-functional biopeptide of the sequence VY (DPPIV and ACE inhibitors, AOXp) can be released as a result of *in silico* protein hydrolysis by digestive enzymes (pepsin, trypsin, and chymotrypsin A). Dipeptide VY was a strong ACE inhibitor isolated from sake (IC_{50} value 7.1 mM) (Saito *et al.* 1994), also identified in hydrolysates obtained by autolysis of wheat bran (IC_{50} value 21 mM), from sardine muscle, which decreased the systolic blood pressure of spontaneously hypertensive rats (Nogata *et al.* 2009; Shamloo *et al.* 2015). VY has also been identified as a DPPIV inhibitor (Lan *et al.* 2015) and an antioxidative peptide in a potato protein hydrolysate (Cheng *et al.* 2010). Among all the mono- and multifunctional biopeptides released from oat globulins, 43% biopeptides were also sensory peptides (Table 1). The A_E and W parameters calculated for the dominant activity (DPPIV inhibitor) for all precursor proteins, following the hydrolysis with three enzymes, were in the range: 0.0212–0.0275 and 0.0313–0.0407, and in the range: 0.0243–0.0312 and 0.0355–0.0460 (sequences without signal peptides). The A_E parameters calculated for four precursor proteins (except AC O49257 and Q38779) were equal to 0.0019 (0.0020 for proteins without signal peptides both when they were active as CaMPDE inhibitors, a renin inhibitor and for antioxidative activity.

CONCLUSIONS

The amino acid sequences of proteins/peptides available in biological databases are used to identify proteins separated by various techniques: electrophoresis, chromatography coupled with mass spectrometry, and to simulate proteolysis, which is the necessary stage especially in designing functional foods. Mono-functional dipeptides with the activity of DPPIV inhibitor (AL, DR, NL, PF, QF, TL and HR) and bi-functional dipeptides (VF, SY, GF, NF, TF, SF and GY) with the enzyme inhibiting activity (ACE and DPPIV), as well as with the activity of a DPPIV inhibitor and glucose uptake stimulating peptide (VL and IL) dominated among the dipeptides present in hydrolysates of oat globulins obtained by *in silico* digestion with three enzymes (pepsin – pH 1.3, trypsin and chymotrypsin A). DPPIV inhibitors (gliptins) belong to the latest groups of drugs used in the treatment of type-2 diabetes, which extend the time of physiological action of incretin GLP-1. Food products can be enriched with peptide inhibitors DPPIV by the application of nano- and ultrafiltration techniques or modified technological processes. Such peptides can modulate the activity of human DPPIV and can be components of functional foods such as antihypertensive peptides. In some countries are available dairy products, such as Calpis (Japan) or Calpico (Europe), Evolus (Finland), which contain antihypertensive peptides (VPP, IPP). Calpis, Calpico are trade names of sour milk, and Evolus is milk fermented with the addition of calcium. All these products contain antihypertensive peptides which were released as a result of β-, κ-casein proteolysis. Biologically active peptides which are contained in these commercial products come from casein (heterogeneous protein), which is from milk proteins.

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