

Food Proteins as Precursors of Bioactive Peptides — Classification Into Families

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The Bioactive Peptides (BIOPEP) database developed at the Department of Food Biochemistry, University of Warmia and Mazury in Olsztyn was used to determine the profiles of the potential biological activity of food proteins and to classify them into families. Proteins whose amino acid sequences contained fragments with a specified activity and which were a potential source of this activity were divided into families. Among the 44 biological activities of peptides included in the BIOPEP database, 23 were selected for analysis. The number of families was diversified. The largest families were composed of proteins — precursors of antihypertensive peptides and dipeptidyl aminopeptidase IV inhibitors as well as those activating ubiquitin-mediated proteolysis and opioid ones. Only a few proteins included in the database contained in their sequences fragments with the following activities: chemotactic, binding and transporting metals and metal ions, stimulating red blood cells synthesis, inducing contractions of smooth muscles, and hemolytic. Highly numerous families were divided into five sub-families according to the value of the frequency of occurrence of fragments exhibiting given activity (*A* parameter).

Key Words: food proteins, bioactive peptides, computational analyses

INTRODUCTION

Karelín advanced a hypothesis that each protein, apart from its basic function, is likely to serve as a reservoir of peptides regulating the vital processes of organisms (Karelín et al., 1998). Hence, an additional criterion for the evaluation of protein value as a potential source of bioactive peptides was postulated (Meisel, 1998; Dziuba et al., 1999b). It constitutes a supplement to the criteria used so far, that considered primarily the content of amino acids indispensable for the proper functioning of organisms, the effect of protein on body mass, allergenic properties (Friedman, 1996; Fukumode and Yoshikawa, 1992), or the content of antinutritional compounds (Bush and Hefle, 1996).

Biologically active (bioactive) motifs in the polypeptide chains of proteins are defined as fragments that remain inactive in sequences of their own precursors, whereas having been released by proteolytic enzymes they may interact with appropriate receptors, thus

regulating the physiological functions of the body. The activity of such peptides may be either favorable or detrimental (Schlimme and Meisel, 1995; Meisel and Bockelmann, 1999).

Investigations carried out at numerous research centers worldwide have resulted in the recognition and detailed characteristics of a vast number of biologically active peptides isolated from tissues and body fluids of a number of organisms, including bacteria, fungi, plants, and animals (Dziuba et al., 1999a; Meisel, 2001; Korhonen and Pihlanto, 2003). The discussed group of compounds is characterized by a high diversity. It contains both simple di- and tripeptides as well as complex linear ones or cyclic oligo- and polypeptides which, additionally, are often modified as a result of glycosylation, phosphorylation, or acylation of amino acid residues. Precursors of a number of biologically active peptides contain, among others, food proteins (Rutherford-Markwick and Moughan, 2005). Protein-derived peptides are likely to affect a decrease in blood pressure, inhibit the activity of proline endopeptidases, stimulate the functions of the immune system, demonstrate opioid agonist and antagonistic activity, induce contractions of smooth muscles, inhibit the process of thrombocyte aggregation, HIV proteinase activity and oxidation processes, exhibit antibacterial, fungicidal and surface activity, bind metal ions and participate in mineral transport, determine the sensory properties, and improve the nutritive value of foods as well as control body mass.

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A growing interest has been observed recently in the use of bioactive peptides for therapeutic purposes, especially in treatment with antibiotics and antimycotic agents, as well as in therapy of the following pathological states: neoplasms, viral inflammations (infections), disorders of the immune systems, neurological and cardiologic disorders (Latham, 1999). Structural motifs occurring in peptides may serve as a source of information to be used while designing new compounds, the so-called 'peptidemimetics' with a similar mechanism of interactions with receptors.

Biologically active peptides are recommended as constituents of the so-called 'functional food' (i.e., food designed in order to obtain the desired functional and biological properties; Korhonen et al., 1998; Hilliam, 2003). Functional foodstuffs are a source of nutrients responsible for the physiological aspects of the proper functioning of the body. In addition, they facilitate the intensification of mental processes. The interest in that type of food has been observed to increase (De Felice, 1995). Investigations are also underway into the inclusion of bioactive peptides and physiological constituents of foods or commercially-obtained nutraceuticals to be used for the production of the so-called 'formones' (*formone* = *food hormone*). Attention is especially paid to peptides lowering blood pressure in a combination with phosphopeptides and immunomodulatory peptides (Gobbetti et al., 2002; Hartmann and Meisel, 2002). In addition, sequences of a variety of peptides can be applied for the restoration of the five basic taste sensations (Kilara and Panyam, 2003).

Biologically active peptides may be products of protein proteolysis in the gastrointestinal tract (Grimble, 1994), or of proteolysis being one of the stages in protein processing. They can also originate from fermented foodstuffs that are gaining significance these days (Campbell-Platt, 1994; Dziuba et al., 1999a). The possibility to release biologically active peptides from proteins, their structural, physiological, and nutritional characteristics have been discussed in many articles (Dziuba et al., 1995, 1999a, 2004, 2005; Dziuba and Minkiewicz 1996; Brody, 2000; Shah, 2000). Amongst food proteins, the best known precursors of bioactive peptides are milk proteins (Meisel, 1998; Pihlanto-Leppälä, 2001; Dziuba et al., 2002; Gobbetti et al., 2002; Kilara and Panyam, 2003; Darewicz et al., 2006; Silva and Malcata, 2005). Both casein as well as whey proteins are rich in motifs demonstrating antihypertensive, opioid, antibacterial, and immunomodulatory activities. An important source of bioactive peptides of animal origin are also muscle and egg proteins (Pihlanto-Leppälä et al., 1998). Collagen and elastin are precursors of peptides with anticoagulant activity (Maruyama et al., 1993), whereas connectin and ovalbumin — of peptides with antihypertensive activity (Fujita et al., 1995). In a variety of plant products, a rich source of bioactive peptides are proteins of soybean,

wheat, rice, and maize (Yoshikawa, et al., 2000; Gibbs et al., 2004).

The appearance of new peptides originating from a variety of sources prompted a need for data ordering and establishing additional criteria for the estimation of the value of proteins as precursors of bioactive peptides. To attain these goals, the profiles of the potential biological activity of proteins (type and location of the bioactive fragment in a protein sequence) were analyzed. New quantitative criteria for protein value estimation, based on the occurrence frequency of bioactive fragments in a protein sequence (A) and the potential activity of protein fragments (B), were also proposed (Dziuba et al., 1999b, 2003). In order to successfully conduct the studies, it was necessary to classify proteins into families with similar biological activity profiles, according to own criterion. The division into families is of primary importance in the aspect of proteolysis design and selection of proteins being the richest source of peptides with a specified activity.

MATERIAL AND METHODS

BIOPEP Database

Investigations addressing the evaluation of proteins as precursors of bioactive peptides and their classification into families and sub-families were carried out based on a database of proteins and bioactive peptides BIOPEP (Dziuba et al., 2003). Both the database of proteins and that of bioactive peptides contain information on their sequences, number of amino acid residues, molecular and isotopic weights, and additional data, such as: function of proteins in biological systems, specified biological activity of a given peptide, and references (www.uwm.edu.pl/biochemia). Of 44 kinds of activity contained in the bioactive peptides (BIOPEP) database and characterizing peptides, analysis was carried out for the following 23: anti-amnesic, anticoagulant, antihypertensive, immunomodulatory, chemotactic, inducing contractions of smooth muscles, toxic, embryotoxic, antioxidant, dipeptidyl aminopeptidase IV inhibitors, opioid, opioid-antagonistic, stimulating the synthesis of red blood cells, hemolytic, binding and transporting metals, ligands of bacterial permease, anorectic, activating ubiquitin-mediated proteolysis, regulating ion flow, neuropeptide inhibitors, regulating the functions of the gastric mucosa, antibacterial and antiviral as well as regulating the action mechanism of phosphoinositol.

Evaluation of Proteins as a Precursors of Bioactive Peptides via the BIOPEP Program

A total of 182 amino acid sequences of proteins compiled in the BIOPEP database were used in

the study. In the estimation of the value of proteins as precursors of bioactive peptides use was made of:

1. The profile of potential biological activity of a given protein defined as: the kind and location of a bioactive fragment in the protein chain
2. The occurrence frequency of bioactive fragments in a protein chain (A):

$$A = \frac{a}{N} \quad (1)$$

where a is the number of amino acid fragments with a given activity in the protein analyzed and N the number of amino acid residues in a polypeptide chain of protein.

The detailed information concerning new criteria of protein evaluation in BIOPEP were described by Dziuba and Iwaniak (2006).

Classification of Proteins

All analyzed proteins included in the database were grouped into families and subfamilies. The occurrence of motifs with a given activity in a protein sequence was adopted as a criterion of affiliation to a given family. Within each family of proteins — precursors of peptides with a specified biological activity — a division was made into sub-families with respect to the occurrence frequency of active fragments in a protein sequence, expressed as the value of parameter A . The parameter was computed using the 'A. B. Y Calculation' option in the BIOPEP program. The division was performed with the use of procedure of the analysis of distributive series, which enabled the appropriate number of proteins to be assigned to a given subfamily (interval). Such intervals are referred to as class intervals, and the differences between the upper and lower limit of the i -th class interval — as interval span h_i :

$$h_i = x_{0i} - x_{0i-1} \quad (2)$$

where x_{0i} and x_{0i-1} ($i = 1, \dots, k$) are the limits of the i -th interval.

The A values of individual proteins were divided into groups using equal interval according to the rules of stem-and-leaf procedure (Lane, 2003) although without use stem-and-leaf notation. The results obtained were compiled as data sets and classified to one of the five class intervals with a constant interval span. Thus, five sub-families were created within each protein family.

RESULTS AND DISCUSSION

Twenty three families of peptide precursors were obtained, representing the following activities: antihypertensive 178 proteins; antithrombotic 82 proteins;

antiamnesic 83 proteins; immunomodulatory 89 proteins; antioxidant 79 proteins; toxic 13 proteins; inducing smooth muscle contraction 2 proteins; chemotactic 6 proteins; embryotoxic 3 proteins; opioid 111 proteins; regulating ion flow 41 proteins; regulating the functions of the gastric mucosa 79 proteins; dipeptidyl aminopeptidase IV inhibitors 148 proteins; activating ubiquitin-mediated proteolysis 124 proteins; regulating the action mechanism of phosphoinositide 28 proteins; neuropeptide inhibitors 71 proteins; ligands of bacterial permease 80 proteins; stimulating red blood cells synthesis 2 proteins; hemolytic 1 protein; anorectic 12 proteins; opioid-antagonistic 6 proteins; binding and transporting metals and metal ions 3 proteins; as well as antibacterial and antiviral 10 proteins. The aforesaid types of activity were selected due to the common occurrence of peptides exhibiting them, and also due to their properties which are considered interesting from the health-promoting or technological point of view. Antihypertensive, activating ubiquitin-mediated proteolysis, opioid fragments and dipeptidyl aminopeptidase IV inhibitors were noticed in the majority of the profiles of potential biological activity of all analyzed protein sequences. Each profile describes the location, kind of activity, and length of a given fragment in the protein sequence. The proteins under scrutiny were characterized by a considerable diversity of profiles. The amino acid sequences of the majority of proteins were found to contain fragments corresponding to peptides with various activities. An exemplary profile of 1432 amino acid residues containing hen collagen (α -1 (ID 1113 in BIOPEP database), highly abundant in biologically active fragments, is presented in Table 1. This may suggest that, apart from its basic structural function, protein can also be a precursor of multiple endogenous biologically active peptides. In the case of hen collagen, the following activities were found to predominate: antiamnesic, antithrombotic, regulating ion flow, and dipeptidyl aminopeptidase IV inhibitors, although peptides exhibiting such activities are not the most numerous group in the BIOPEP database. A considerable part of the fragments found appears to be di- and tripeptides. That information is especially important taking into account the absorption of those peptides from the gastrointestinal tract to blood. Di- and tripeptides are better absorbable than free amino acids (Vermeirssen et al., 2004). Short peptides cross the intestinal barrier more quickly than free amino acids, which affects the optimization of water metabolism in the body, also having the importance in designing diets for special purposes, e.g., hydrolysate-based medical diets for sportsmen (Schmidl et al., 1994). Some of bioactive peptides that were found within the profiles of potential biological activity of 182 analyzed proteins are multifunctional. Biologically active dipeptides with the following sequence: GP and PG may serve as the examples (Table 1). They reveal activities such as

Table 1. Profile of potential biological activity of hen α -collagen [BIOPEP database ID 1113: collagen alpha 1(I) chain precursor, chicken (*Gallus gallus*)].

Protein Sequence, BIOPEP Database : 1113

EGFEEDIQTGSCVQDGLTYNDKDVWKPEPCQICVCDSGNII.CDEVICEDTSDCPNAEIPFGECPCICPDVDASPVY
 PESAGVEGPKGDTGPRGDRGLPGPPGRDGI PGQPGLPGPPGPPGLGGNFAPQMSYGYDEKSAGVAVPGPM
 GPAGPRGLPGPPGAPGPGQFGPPGEPGEPGASGPMGRGPAGPPGKNGDDGEAGKPGRPGQRPQGPQARG
 LPGTAGLPGMKGHRGFSGLDGA.KGQPGPAGPKGEPGSPGENGAPQMGRGLPGERGRPGSPGAGARGNDG
 APGAAGPPGPTGPAGPPGPGGAAGAKGETGPQGARQSEGPQGSRGEPGPPGPA.GA.AGPA.GNPG.ADGQPG.AKG
 ATGAPGAGAPGPGARGSPGPGQPSGAPGPKGNSGEPGAPGNKGDGTGAKGEPGAGVQGPAGGEEGKRGA
 RGEPGAGLPGPAGERGAPGSRGFP.GADGIAGPKGPPGERGSPGAVGPKGSPGEAGRPG.EAGLP.GAKGLTGSPG
 SP.GPDGKTGPPGAPGQDGRPGAPPPGARGQAGV.MGFP.GPKGAAGEPGKPGERGAPGPPGAVGAAGKDGEA
 GAQQGPPGPTGPAGERGEQGPAGAPGFQGLPGAPPPGEAGKPGEQVPGNAGAPGAPAGARGERGPPGERGVQ
 GPPGPGQPRGANGAPGNDGAKGDAGAPGAPGNEGPPGLEMPGERGAAGLP.GAKGDRGDPGPKGADGAPGK
 DGLRGLTGPIPPGAPAGPGDKGEAGPPGAPGPTGARGAPGDRGEPGPPGAPGAGPPGADGQPGAKGETGDA
 GAKGDAGPPGAPGPTGAPGAPGZYGAPGPKGARGSPGPPGATGFP.GAAGRVGPPGPSNIGLP.GPPGAPGKZG
 SKGPRGETGPAGRPGEPPGAPGPPGPPGEGKSPGADGPIGAPGTPGPGIAGQRGVVGLPGQRGERGFPGLPGPS
 GEPGKQGPSGASGERGPPGMPGLAGPPGEAGRGAPG.AGAPGRDGAAGPKGDRGETGAPGPPGAPGAP
 GAPGPGVGPAGKNGDRGETGPAGAPGPPGAPARGAPGAPGQPRGDKGETGEQGD.RGMKGHRGFSGLQGP.PPP
 GAPGEQGPSGASGPAGPRGPPGSAGAAGKDGL.NGLPGIPGPPGPRGRTGEVGPV.GPPGPPGPPGPPGPPSGGDFD
 SFLPQPPQEK.AHDGGRYR.RADDAN
 VM.RDRLEVDITLTKLSLQQIENIRSPGTRKNPARTCRDLK.MCHGDWKSGEY.WIDPNQCCNLDAIKVVCNME
 TGECTCYPTQTATIAQKNWYLSKNPKEKKHVWFGETMSDGFQFEYGGEGSNPADV.AIQLTFLRLMSTEATQNV
 TYHCKNSVAYMDHDTGNLKKALLLQ.GANEIEIRAEGNSRFTYGVTE.DGCTSI.TGAWGKT.VIEYKTKTSRLPII
 DLAPMDVGAPDQFEGIDIGPVCFL

Peptides

ID	Source and location	Activity	No.	Sequence	Location
3459	Synthetic	Antiamestic	52	PGP	[97-99],[112-114],[115-117],[118-120],[145-147],[157-159],[163-165],[214-216],[247-249],[280-282],[301-303],[340-342],[343-345],[304-306],[418-420],[427-429],[442-444],[448-450],[514-516],[523-525],[532-534],[550-552],[568-570],[589-591],[613-615],[637-639],[658-660],[715-717],[739-741],[754-756],[772-774],[775-777],[808-810],[817-819],[826-828],[853-855],[862-864],[865-867],[889-891],[895-897],[916-918],[943-945],[964-966],[1021-1023],[1045-1047],[1087-1089],[1126-1128],[1132-1134],[1147-1149],[1150-1152],[1153-1155],[1156-1158],[97-98],[100-101],[106-107],[109-110],[112-113],[115-116],[118-119],[121-122],[145-146],[157-158],[169-161],[163-164],[172-173],[175-176],[178-179],[193-194],[205-206],[208-209],[214-215],[223-224],[229-230],[247-248],[256-257],[259-260],[265-266],[274-275],[280-281],[295-296],[301-302],[310-311],[313-314],[340-341],[343-344],[355-356],[361-362],[370-371],[376-377],[379-380],[394-395],[403-404],[406-407],[418-419],[427-428],[442-443],[448-449],[457-458],[463-464],[475-476],[481-482],[490-491],[496-497],[502-503],[511-512],[514-515],[523-524],[532-533],[538-539],[550-551],[559-560],[562-563],[568-569],[571-572],[589-590],[607-608],[613-614],[619-620],[625-626],[631-632],[637-638],[649-650],[658-659],[670-671],[682-683],[685-686],[691-692],[697-698],[706-707],[715-716],[724-725],[739-740],[745-746],[754-755],[766-767],[772-773],[775-776],[784-785],[790-791],[808-809],[817-818],[826-827],[838-839],[844-845],[853-854],[862-863],[865-866],[866-867],[889-890],[895-896],[898-899],[904-905],[913-914],[916-917],[931-932],[940-941],[943-944],[949-950],[964-965],[970-971],[976-977],[985-986],[991-992],[1012-1013],[1015-1016],[1018-1019],[1021-1022],[1045-1046],[1087-1088],[1090-1091],[1093-1094],[1111-1112],[1126-1127],[1132-1133],[1147-1148],[1150-1151],[1153-1154],[1156-1157],[83-84],[89-90],[98-99],[113-114],[116-117],[119-120],[146-147],[149-150],[152-153],[158-159],[164-165],[179-171],[182-183],[185-186],[188-189],[191-192],[212-213],[215-216],[248-249],[251-252],[269-270],[281-282],[284-285],[292-300],[302-303],[305-306],[308-309],[323-324],[332-333],[341-342],[344-345],[350-351],[383-384],[386-387],[389-390],[395-396],[419-420],[425-426],[428-429],[443-444],[449-450],[470-471],[473-474],[485-486],[515-516],[521-522],[524-525],[533-534],[536-537],[551-552],[569-570],[587-588],[590-591],[593-594],[602-603],[614-615],[617-618],[638-639],[656-657],[659-660],[662-663],[689-690],[716-717],[734-735],[737-738],[740-741],[752-753],[755-756],[758-759],[773-774],[776-777],[782-783],[806-807],[809-810],[812-813],[818-819],[827-828],[836-837],[851-852],[854-855],[863-864],[866-867],[875-876],[881-882],[890-
3460	Synthetic	Antiamestic	126	PG	[97-98],[100-101],[106-107],[109-110],[112-113],[115-116],[118-119],[121-122],[145-146],[157-158],[169-161],[163-164],[172-173],[175-176],[178-179],[193-194],[205-206],[208-209],[214-215],[223-224],[229-230],[247-248],[256-257],[259-260],[265-266],[274-275],[280-281],[295-296],[301-302],[310-311],[313-314],[340-341],[343-344],[355-356],[361-362],[370-371],[376-377],[379-380],[394-395],[403-404],[406-407],[418-419],[427-428],[442-443],[448-449],[457-458],[463-464],[475-476],[481-482],[490-491],[496-497],[502-503],[511-512],[514-515],[523-524],[532-533],[538-539],[550-551],[559-560],[562-563],[568-569],[571-572],[589-590],[607-608],[613-614],[619-620],[625-626],[631-632],[637-638],[649-650],[658-659],[670-671],[682-683],[685-686],[691-692],[697-698],[706-707],[715-716],[724-725],[739-740],[745-746],[754-755],[766-767],[772-773],[775-776],[784-785],[790-791],[808-809],[817-818],[826-827],[838-839],[844-845],[853-854],[862-863],[865-866],[866-867],[889-890],[895-896],[898-899],[904-905],[913-914],[916-917],[931-932],[940-941],[943-944],[949-950],[964-965],[970-971],[976-977],[985-986],[991-992],[1012-1013],[1015-1016],[1018-1019],[1021-1022],[1045-1046],[1087-1088],[1090-1091],[1093-1094],[1111-1112],[1126-1127],[1132-1133],[1147-1148],[1150-1151],[1153-1154],[1156-1157],[83-84],[89-90],[98-99],[113-114],[116-117],[119-120],[146-147],[149-150],[152-153],[158-159],[164-165],[179-171],[182-183],[185-186],[188-189],[191-192],[212-213],[215-216],[248-249],[251-252],[269-270],[281-282],[284-285],[292-300],[302-303],[305-306],[308-309],[323-324],[332-333],[341-342],[344-345],[350-351],[383-384],[386-387],[389-390],[395-396],[419-420],[425-426],[428-429],[443-444],[449-450],[470-471],[473-474],[485-486],[515-516],[521-522],[524-525],[533-534],[536-537],[551-552],[569-570],[587-588],[590-591],[593-594],[602-603],[614-615],[617-618],[638-639],[656-657],[659-660],[662-663],[689-690],[716-717],[734-735],[737-738],[740-741],[752-753],[755-756],[758-759],[773-774],[776-777],[782-783],[806-807],[809-810],[812-813],[818-819],[827-828],[836-837],[851-852],[854-855],[863-864],[866-867],[875-876],[881-882],[890-
3461	Synthetic	Antiamestic	123	GP	[83-84],[89-90],[98-99],[113-114],[116-117],[119-120],[146-147],[149-150],[152-153],[158-159],[164-165],[179-171],[182-183],[185-186],[188-189],[191-192],[212-213],[215-216],[248-249],[251-252],[269-270],[281-282],[284-285],[292-300],[302-303],[305-306],[308-309],[323-324],[332-333],[341-342],[344-345],[350-351],[383-384],[386-387],[389-390],[395-396],[419-420],[425-426],[428-429],[443-444],[449-450],[470-471],[473-474],[485-486],[515-516],[521-522],[524-525],[533-534],[536-537],[551-552],[569-570],[587-588],[590-591],[593-594],[602-603],[614-615],[617-618],[638-639],[656-657],[659-660],[662-663],[689-690],[716-717],[734-735],[737-738],[740-741],[752-753],[755-756],[758-759],[773-774],[776-777],[782-783],[806-807],[809-810],[812-813],[818-819],[827-828],[836-837],[851-852],[854-855],[863-864],[866-867],[875-876],[881-882],[890-

(Continued)

Table 1. Continued.

					891],[893-894],[896-897],[908-909],[917-918],[944-945],[953-954],[962-963],[965-966],[968-969],[974-975],[998-999],[1007-1008],[1010-1011],[1022-1023],[1025-1026],[1037-1038],[1040-1041],[1043-1044],[1046-1047],[1052-1053],[1055-1056],[1058-1059],[1085-1086],[1088-1089],[1097-1098],[1103-1104],[1106-1107],[1109-1110],[1127-1128],[1130-1131],[1133-1134],[1142-1143],[1145-1146],[1148-1149],[1151-1152],[1154-1155],[1157-1158],[1427-1428],[1323-1324],[1404-1405]
3257	β -Lg [148-149] ¹	Antihypertensive	2	RI	
3258	β -Lg [147-148] ¹	Antihypertensive	2	IR	[1212-1213],[1366-1367]
3370	β -Ca [177-179] ²	Antihypertensive	1	AVP	[143-145]
3378	Sardine Muscle	Antihypertensive	5	GRP	[206-208],[278-280],[494-496],[530-532],[884-886]
3380	Sardine Muscle	Antihypertensive	1	RY	[1181-1182]
3393	α -CN [25-27] ¹	Antihypertensive	1	FAP	[127-129]
3486	Sake and Sake Lees	Antihypertensive	2	VW	[23-24],[1291-1292]
3488	Sake and Sake Lees	Antihypertensive	1	YW	[1241-1242]
3489	Sake and Sake Lees	Antihypertensive	1	RF	[1373-1374]
3492	Sake and Sake Lees	Antihypertensive	3	VY	[74-75],[1256-1257],[1267-1268]
3502	Bsa [221-222] ¹	Antihypertensive	7	FP	[312-313],[378-379],[462-463],[549-550],[648-649],[843-844],[939-940]
3505	β -Ca [59-61] ²	Antihypertensive	2	VYP	[74-76],[1267-1269]
3506	β -Ca [18-20] ²	Antihypertensive	3	GKP	[203-205],[560-562],[623-625]
3532	Sake and Sake Lees	Antihypertensive	1	GY	[134-135]
3537	Sake and Sake Lees	Antihypertensive	9	PR	[90-91],[153-154],[186-187],[270-271],[663-664],[876-877],[1059-1060],[1107-1108],[1134-1135]
3546	Zein Hydrolysate	Antihypertensive	1	VAY	[1341-1343]
3547	Zein Hydrolysate	Antihypertensive	1	IRA	[1366-1368]
3550	α -CN [78-79]; [81-82] ¹	Antihypertensive	1	YL	[1280-1281]
3553	κ -Ca [38-39] ¹	Antihypertensive	3	YG	[133-134],[1305-1306],[1376-1377]
3563	α -CN [130-131]; [145-146] ¹	Antihypertensive	1	AY	[1342-1343]
3606	Hemoglobin α -Chain [24-25]	Antihypertensive	2	YP	[75-76],[1268-1269]
3121	Collagen A1-Chain [435-438]	Antithrombotic	2	DGEA	[199-202],[580-583]
3122	Collagen A1-Chain [434-438]	Antithrombotic	1	KDGEA	[579-583]
3283	Synthetic	Antithrombotic	123	GP	[83-84],[89-90],[98-99],[113-114],[116-117],[119-120],[146-147],[149-150],[152-153],[158-159],[164-165],[170-171],[182-183],[185-186],[188-189],[191-192],[212-213],[215-216],[248-249],[251-252],[269-270],[281-282],[284-285],[299-300],[302-303],[305-306],[308-309],[323-324],[332-333],[341-342],[344-345],[350-351],[383-384],[386-387],[389-390],[395-396],[419-420],[425-426],[428-429],[443-444],[449-450],[470-471],[473-474],[485-486],[515-516],[521-522],[524-525],[533-534],[536-537],[551-552],[569-570],[587-588],[590-591],[593-594],[602-603],[614-615],[617-618],[638-639],[656-657],[659-660],[662-663],[689-690],[716-717],[734-735],[737-738],[740-741],[752-753],[755-756],[758-759],[773-774],[776-777],[782-783],[806-807],[809-810],[812-813],[818-819],[827-828],[836-837],[851-852],[854-855],[863-864],[866-867],[875-876],[881-882],[890-891],[893-894],[896-897],[908-909],[917-918],[944-945],[953-954],[962-963],[965-966],[968-969],[974-975],[998-999],[1007-1008],[1010-1011],[1022-1023],[1025-1026],[1037-1038],[1040-1041],[1043-1044],[1046-1047],[1052-1053],[1055-1056],[1058-1059],[1085-1086],[1088-1089],[1097-1098],[1103-1104],[1106-1107],[1109-1110],[1127-1128],[1130-1131],[1133-1134],[1142-1143],[1145-1146],[1148-1149],[1151-1152],[1154-1155],[1157-1158],[1427-1428]

(Continued)

Table 1. Continued.

3284	Synthetic	Antithrombotic	52	PGP	[97-99],[112-114],[115-117],[118-120],[145-147],[157-159],[163-165],[214-216],[247-249],[280-282],[301-303],[340-342],[343-345],[394-396],[418-420],[427-429],[442-444],[448-450],[514-516],[523-525],[532-534],[550-552],[568-570],[589-591],[613-615],[637-639],[658-660],[715-717],[739-741],[754-756],[772-774],[775-777],[808-810],[817-819],[826-828],[853-855],[862-864],[865-867],[889-891],[895-897],[916-918],[943-945],[964-966],[1021-1023],[1045-1047],[1087-1089],[1126-1128],[1132-1134],[1147-1149],[1150-1152],[1153-1155],[1156-1158]
3285	Synthetic	Antithrombotic	126	PG	[97-98],[100-101],[106-107],[109-110],[112-113],[115-116],[118-119],[121-122],[145-146],[157-158],[160-161],[163-164],[172-173],[175-176],[178-179],[193-194],[205-206],[208-209],[214-215],[223-224],[229-230],[247-248],[256-257],[259-260],[265-266],[274-275],[280-281],[295-296],[301-302],[310-311],[313-314],[340-341],[343-344],[355-356],[361-362],[370-371],[376-377],[379-380],[394-395],[403-404],[406-407],[418-419],[427-428],[442-443],[448-449],[457-458],[463-464],[475-476],[481-482],[490-491],[496-497],[502-503],[511-512],[514-515],[523-524],[532-533],[538-539],[550-551],[559-560],[562-563],[568-569],[571-572],[589-590],[607-608],[613-614],[619-620],[625-626],[631-632],[637-638],[649-650],[658-659],[670-671],[682-683],[685-686],[691-692],[697-698],[706-707],[715-716],[724-725],[739-740],[745-746],[754-755],[766-767],[772-773],[775-776],[784-785],[790-791],[808-809],[817-818],[826-827],[838-839],[844-845],[853-854],[862-863],[865-866],[886-887],[889-890],[895-896],[898-899],[904-905],[913-914],[916-917],[931-932],[940-941],[943-944],[949-950],[964-965],[970-971],[976-977],[985-986],[991-992],[1012-1013],[1015-1016],[1018-1019],[1021-1022],[1045-1046],[1087-1088],[1090-1091],[1093-1094],[1111-1112],[1126-1127],[1132-1133],[1147-1148],[1150-1151],[1153-1154],[1156-1157],[1305-1307]
3741	α -La [18-20] ^a	Immuno-modulating	1	YGG	[133-134],[1305-1306],[1376-1377]
3770	α -La [18-19] ^a	Immuno-modulating	3	YG	[133-134],[1305-1306],[1376-1377]
2872	Lipotropin [14-17]	Opioid	1	NAGA	[633-636]
2882	α -La [50-51] ^a	Opioid	3	YG	[133-134],[1305-1306],[1376-1377]
3474	α -La [91-92] ^a	Opioid	1	YL	[1280-1281]
3098	β -Cn [91-93] ^a	Immuno-stimulating	1	GVM	[545-547]
2753	Synthetic	Regulating ion flow	123	GP	[83-84],[89-90],[98-99],[113-114],[116-117],[119-120],[146-147],[149-150],[152-153],[158-159],[164-165],[170-171],[182-183],[185-186],[188-189],[191-192],[212-213],[215-216],[248-249],[251-252],[269-270],[281-282],[284-285],[299-300],[302-303],[305-306],[308-309],[323-324],[332-333],[341-342],[344-345],[350-351],[383-384],[386-387],[389-390],[395-396],[419-420],[425-426],[428-429],[443-444],[449-450],[470-471],[473-474],[485-486],[515-516],[521-522],[524-525],[533-534],[536-537],[551-552],[569-570],[587-588],[590-591],[593-594],[602-603],[614-615],[617-618],[638-639],[656-657],[659-660],[662-663],[689-690],[716-717],[734-735],[737-738],[740-741],[752-753],[755-756],[758-759],[773-774],[776-777],[782-783],[806-807],[809-810],[812-813],[818-819],[827-828],[836-837],[851-852],[854-855],[863-864],[866-867],[875-876],[881-882],[890-891],[893-894],[896-897],[908-909],[917-918],[944-945],[953-954],[962-963],[965-966],[968-969],[974-975],[998-999],[1007-1008],[1010-1011],[1022-1023],[1025-1026],[1037-1038],[1040-1041],[1043-1044],[1046-1047],[1052-1053],[1055-1056],[1058-1059],[1085-1086],[1088-1089],[1097-1098],[1103-1104],[1106-1107],[1109-1110],[1127-1128],[1130-1131],[1133-1134],[1142-1143],[1145-1146],[1148-1149],[1151-1152],[1154-1155],[1157-1158],[1427-1428]
2754	Synthetic	Regulating ion flow	126	PG	[97-98],[100-101],[106-107],[109-110],[112-113],[115-116],[118-119],[121-122],[145-146],[157-158],[160-161],[163-164],[172-173],[175-176],[178-179],[193-194],[205-206],[208-209],[214-215],[223-224],[229-230],[247-248],[256-257],[259-260],[265-266],[274-275],[280-281],[295-296],[301-302],[310-311],[313-314],[340-341],[343-344],[355-356],[361-362],[370-371],[376-377],[379-380],[394-395],[403-404],[406-407],[418-419],[427-428],[442-443],[448-449],[457-458],[463-464],[475-476],[481-482],[490-491],[496-497],[502-503],[511-512],[514-515],[523-524],[532-533],[538-539],[550-551],[559-560],[562-563],[568-569],[571-572],[589-590],[607-608],[613-614],[619-620],[625-626],[631-632],[637-638],[649-650],[658-659],[670-671],[682-683],[685-686],[691-692],[697-698],[706-707],[715-716],[724-725],[739-740],[745-746],[754-755],[766-767],[772-773],[775-776],[784-785],[790-791],[808-809],[817-818],[826-827],[838-839],[844-845],[853-854],[862-863],[865-866],[886-887],[889-890],[895-896],[898-899],[904-905],[913-914],[916-917],[931-932],[940-941],[943-944],[949-950],[964-965],[970-971],[976-977],[985-986],[991-992],[1012-1013],[1015-1016],[1018-1019],[1021-1022],[1045-1046],[1087-1088],[1090-1091],[1093-1094],[1111-1112],[1126-1127],[1132-1133],[1147-1148],[1150-1151],[1153-1154],[1156-1157]

(Continued)

Table 1. Continued.

2756	Synthetic	Regulating ion flow	52	PGP	[97-99],[112-114],[115-117],[118-120],[145-147],[157-159],[163-165],[211-216],[247-249],[280-282],[301-303],[340-342],[343-345],[394-396],[418-420],[427-429],[442-444],[448-450],[514-516],[523-525],[532-534],[550-552],[568-570],[589-591],[613-615],[637-639],[658-660],[715-717],[739-741],[754-756],[772-774],[775-777],[808-810],[817-819],[826-828],[853-855],[862-864],[865-867],[889-891],[895-897],[916-918],[943-945],[964-966],[1021-1023],[1045-1047],[1087-1089],[1126-1128],[1132-1134],[1147-1149],[1150-1152],[1153-1155],[1156-1158],[1288-1289],[1352-1353]
3751	β -Endorphin	Bacterial permease ligand	2	KK	
2890	β -Endorphin	Neuropeptide inhibitor	10	GQ	[107-108],[209-210],[245-246],[266-267],[359-360],[527-528],[542-543],[788-789],[923-924],[932-933]
3040	Collagen Hydrolysate	Fibrinogen & trombin coagulation inhibitor	9	GPRG	[89-92],[152-155],[185-188],[269-272],[662-665],[875-878],[1058-1061],[1106-1109],[1133-1136]
3041	Collagen Hydrolysate	Fibrinogen & trombin coagulation inhibitor	2	GPRGP	[185-189],[1106-1110]
3042	Collagen Hydrolysate	Fibrinogen & trombin coagulation inhibitor	1	GPRGPA	[185-190]
3044	Collagen Hydrolysate	Fibrinogen & trombin coagulation inhibitor	1	GPRGPP	[1106-1111]
3047	Collagen Hydrolysate	Fibrinogen & trombin coagulation inhibitor	9	GPR	[89-91],[152-154],[185-187],[269-271],[662-664],[875-877],[1058-1060],[1106-1108],[1133-1135]
3169	<i>Actinomycetes</i>	Dipeptidyl aminopeptidase IV inhibitor	123	GP	[83-84],[89-90],[98-99],[113-114],[116-117],[119-120],[146-147],[149-150],[152-153],[158-159],[164-165],[170-171],[182-183],[185-186],[188-189],[191-192],[212-213],[215-216],[248-249],[251-252],[269-270],[281-282],[284-285],[299-300],[302-303],[305-306],[308-309],[323-324],[332-333],[341-342],[344-345],[350-351],[383-384],[386-387],[389-390],[395-396],[419-420],[425-426],[428-429],[443-444],[449-450],[470-471],[473-474],[485-486],[515-516],[521-522],[524-525],[533-534],[536-537],[551-552],[569-570],[587-588],[590-591],[593-594],[602-603],[614-615],[617-618],[638-639],[656-657],[659-660],[662-663],[689-690],[716-717],[734-735],[737-738],[740-741],[752-753],[755-756],[758-759],[773-774],[776-777],[782-783],[806-807],[809-810],[812-813],[818-819],[827-828],[836-837],[851-852],[854-855],[863-864],[866-867],[875-876],[881-882],[890-891],[893-894],[896-897],[908-909],[917-918],[944-945],[953-954],[962-963],[965-966],[968-969],[974-975],[998-999],[1007-1008],[1010-1011],[1022-1023],[1025-1026],[1037-1038],[1040-1041],[1043-1044],[1046-1047],[1052-1053],[1055-1056],[1058-1059],[1085-1086],[1088-1089],[1097-1098],[1103-1104],[1106-1107],[1109-1110],[1127-1128],[1130-1131],[1133-1134],[1142-1143],[1145-1146],[1148-1149],[1151-1152],[1154-1155],[1157-1158],[1162-1163],[1164-1165],[1167-1168],[1170-1171],[1173-1174],[1176-1177],[1179-1180],[1183-1184],[1187-1188],[1190-1191],[1193-1194],[1197-1198],[1200-1201],[1203-1204],[1206-1207],[1209-1210],[1213-1214],[1216-1217],[1220-1221],[1223-1224],[1227-1228],[1230-1231],[1233-1234],[1237-1238],[1240-1241],[1243-1244],[1247-1248],[1250-1251],[1253-1254],[1257-1258],[1260-1261],[1263-1264],[1267-1268],[1270-1271],[1273-1274],[1277-1278],[1280-1281],[1283-1284],[1287-1288],[1290-1291],[1293-1294],[1297-1298],[1300-1301],[1303-1304],[1307-1308],[1310-1311],[1313-1314],[1317-1318],[1320-1321],[1323-1324],[1327-1328],[1330-1331],[1333-1334],[1337-1338],[1340-1341],[1343-1344],[1347-1348],[1350-1351],[1353-1354],[1357-1358],[1360-1361],[1363-1364],[1367-1368],[1370-1371],[1373-1374],[1377-1378],[1380-1381],[1383-1384],[1387-1388],[1390-1391],[1393-1394],[1397-1398],[1400-1401],[1403-1404],[1407-1408],[1410-1411],[1413-1414],[1417-1418],[1420-1421],[1423-1424],[1427-1428],[1430-1431],[1433-1434],[1437-1438],[1440-1441],[1443-1444],[1447-1448],[1450-1451],[1453-1454],[1457-1458],[1460-1461],[1463-1464],[1467-1468],[1470-1471],[1473-1474],[1477-1478],[1480-1481],[1483-1484],[1487-1488],[1490-1491],[1493-1494],[1497-1498],[1500-1501],[1503-1504],[1507-1508],[1510-1511],[1513-1514],[1517-1518],[1520-1521],[1523-1524],[1527-1528],[1530-1531],[1533-1534],[1537-1538],[1540-1541],[1543-1544],[1547-1548],[1550-1551],[1553-1554],[1557-1558],[1560-1561],[1563-1564],[1567-1568],[1570-1571],[1573-1574],[1577-1578],[1580-1581],[1583-1584],[1587-1588],[1590-1591],[1593-1594],[1597-1598],[1600-1601],[1603-1604],[1607-1608],[1610-1611],[1613-1614],[1617-1618],[1620-1621],[1623-1624],[1627-1628],[1630-1631],[1633-1634],[1637-1638],[1640-1641],[1643-1644],[1647-1648],[1650-1651],[1653-1654],[1657-1658],[1660-1661],[1663-1664],[1667-1668],[1670-1671],[1673-1674],[1677-1678],[1680-1681],[1683-1684],[1687-1688],[1690-1691],[1693-1694],[1697-1698],[1700-1701],[1703-1704],[1707-1708],[1710-1711],[1713-1714],[1717-1718],[1720-1721],[1723-1724],[1727-1728],[1730-1731],[1733-1734],[1737-1738],[1740-1741],[1743-1744],[1747-1748],[1750-1751],[1753-1754],[1757-1758],[1760-1761],[1763-1764],[1767-1768],[1770-1771],[1773-1774],[1777-1778],[1780-1781],[1783-1784],[1787-1788],[1790-1791],[1793-1794],[1797-1798],[1800-1801],[1803-1804],[1807-1808],[1810-1811],[1813-1814],[1817-1818],[1820-1821],[1823-1824],[1827-1828],[1830-1831],[1833-1834],[1837-1838],[1840-1841],[1843-1844],[1847-1848],[1850-1851],[1853-1854],[1857-1858],[1860-1861],[1863-1864],[1867-1868],[1870-1871],[1873-1874],[1877-1878],[1880-1881],[1883-1884],[1887-1888],[1890-1891],[1893-1894],[1897-1898],[1900-1901],[1903-1904],[1907-1908],[1910-1911],[1913-1914],[1917-1918],[1920-1921],[1923-1924],[1927-1928],[1930-1931],[1933-1934],[1937-1938],[1940-1941],[1943-1944],[1947-1948],[1950-1951],[1953-1954],[1957-1958],[1960-1961],[1963-1964],[1967-1968],[1970-1971],[1973-1974],[1977-1978],[1980-1981],[1983-1984],[1987-1988],[1990-1991],[1993-1994],[1997-1998],[2000-2001],[2003-2004],[2007-2008],[2010-2011],[2013-2014],[2017-2018],[2020-2021],[2023-2024],[2027-2028],[2030-2031],[2033-2034],[2037-2038],[2040-2041],[2043-2044],[2047-2048],[2050-2051],[2053-2054],[2057-2058],[2060-2061],[2063-2064],[2067-2068],[2070-2071],[2073-2074],[2077-2078],[2080-2081],[2083-2084],[2087-2088],[2090-2091],[2093-2094],[2097-2098],[2100-2101],[2103-2104],[2107-2108],[2110-2111],[2113-2114],[2117-2118],[2120-2121],[2123-2124],[2127-2128],[2130-2131],[2133-2134],[2137-2138],[2140-2141],[2143-2144],[2147-2148],[2150-2151],[2153-2154],[2157-2158],[2160-2161],[2163-2164],[2167-2168],[2170-2171],[2173-2174],[2177-2178],[2180-2181],[2183-2184],[2187-2188],[2190-2191],[2193-2194],[2197-2198],[2200-2201],[2203-2204],[2207-2208],[2210-2211],[2213-2214],[2217-2218],[2220-2221],[2223-2224],[2227-2228],[2230-2231],[2233-2234],[2237-2238],[2240-2241],[2243-2244],[2247-2248],[2250-2251],[2253-2254],[2257-2258],[2260-2261],[2263-2264],[2267-2268],[2270-2271],[2273-2274],[2277-2278],[2280-2281],[2283-2284],[2287-2288],[2290-2291],[2293-2294],[2297-2298],[2300-2301],[2303-2304],[2307-2308],[2310-2311],[2313-2314],[2317-2318],[2320-2321],[2323-2324],[2327-2328],[2330-2331],[2333-2334],[2337-2338],[2340-2341],[2343-2344],[2347-2348],[2350-2351],[2353-2354],[2357-2358],[2360-2361],[2363-2364],[2367-2368],[2370-2371],[2373-2374],[2377-2378],[2380-2381],[2383-2384],[2387-2388],[2390-2391],[2393-2394],[2397-2398],[2400-2401],[2403-2404],[2407-2408],[2410-2411],[2413-2414],[2417-2418],[2420-2421],[2423-2424],[2427-2428],[2430-2431],[2433-2434],[2437-2438],[2440-2441],[2443-2444],[2447-2448],[2450-2451],[2453-2454],[2457-2458],[2460-2461],[2463-2464],[2467-2468],[2470-2471],[2473-2474],[2477-2478],[2480-2481],[2483-2484],[2487-2488],[2490-2491],[2493-2494],[2497-2498],[2500-2501],[2503-2504],[2507-2508],[2510-2511],[2513-2514],[2517-2518],[2520-2521],[2523-2524],[2527-2528],[2530-2531],[2533-2534],[2537-2538],[2540-2541],[2543-2544],[2547-2548],[2550-2551],[2553-2554],[2557-2558],[2560-2561],[2563-2564],[2567-2568],[2570-2571],[2573-2574],[2577-2578],[2580-2581],[2583-2584],[2587-2588],[2590-2591],[2593-2594],[2597-2598],[2600-2601],[2603-2604],[2607-2608],[2610-2611],[2613-2614],[2617-2618],[2620-2621],[2623-2624],[2627-2628],[2630-2631],[2633-2634],[2637-2638],[2640-2641],[2643-2644],[2647-2648],[2650-2651],[2653-2654],[2657-2658],[2660-2661],[2663-2664],[2667-2668],[2670-2671],[2673-2674],[2677-2678],[2680-2681],[2683-2684],[2687-2688],[2690-2691],[2693-2694],[2697-2698],[2700-2701],[2703-2704],[2707-2708],[2710-2711],[2713-2714],[2717-2718],[2720-2721],[2723-2724],[2727-2728],[2730-2731],[2733-2734],[2737-2738],[2740-2741],[2743-2744],[2747-2748],[2750-2751],[2753-2754],[2757-2758],[2760-2761],[2763-2764],[2767-2768],[2770-2771],[2773-2774],[2777-2778],[2780-2781],[2783-2784],[2787-2788],[2790-2791],[2793-2794],[2797-2798],[2800-2801],[2803-2804],[2807-2808],[2810-2811],[2813-2814],[2817-2818],[2820-2821],[2823-2824],[2827-2828],[2830-2831],[2833-2834],[2837-2838],[2840-2841],[2843-2844],[2847-2848],[2850-2851],[2853-2854],[2857-2858],[2860-2861],[2863-2864],[2867-2868],[2870-2871],[2873-2874],[2877-2878],[2880-2881],[2883-2884],[2887-2888],[2890-2891],[2893-2894],[2897-2898],[2900-2901],[2903-2904],[2907-2908],[2910-2911],[2913-2914],[2917-2918],[2920-2921],[2923-2924],[2927-2928],[2930-2931],[2933-2934],[2937-2938],[2940-2941],[2943-2944],[2947-2948],[2950-2951],[2953-2954],[2957-2958],[2960-2961],[2963-2964],[2967-2968],[2970-2971],[2973-2974],[2977-2978],[2980-2981],[2983-2984],[2987-2988],[2990-2991],[2993-2994],[2997-2998],[3000-3001],[3003-3004],[3007-3008],[3010-3011],[3013-3014],[3017-3018],[3020-3021],[3023-3024],[3027-3028],[3030-3031],[3033-3034],[3037-3038],[3040-3041],[3043-3044],[3047-3048],[3050-3051],[3053-3054],[3057-3058],[3060-3061],[3063-3064],[3067-3068],[3070-3071],[3073-3074],[3077-3078],[3080-3081],[3083-3084],[3087-3088],[3090-3091],[3093-3094],[3097-3098],[3100-3101],[3103-3104],[3107-3108],[3110-3111],[3113-3114],[3117-3118],[3120-3121],[3123-3124],[3127-3128],[3130-3131],[3133-3134],[3137-3138],[3140-3141],[3143-3144],[3147-3148],[3150-3151],[3153-3154],[3157-3158],[3160-3161],[3163-3164],[3167-3168],[3170-3171],[3173-3174],[3177-3178],[3180-3181],[3183-3184],[3187-3188],[3190-3191],[3193-3194],[3197-3198],[3200-3201],[3203-3204],[3207-3208],[3210-3211],[3213-3214],[3217-3218],[3220-3221],[3223-3224],[3227-3228],[3230-3231],[3233-3234],[3237-3238],[3240-3241],[3243-3244],[3247-3248],[3250-3251],[3253-3254],[3257-3258],[3260-3261],[3263-3264],[3267-3268],[3270-3271],[3273-3274],[3277-3278],[3280-3281],[3283-3284],[3287-3288],[3290-3291],[3293-3294],[3297-3298],[3300-3301],[3303-3304],[3307-3308],[3310-3311],[3313-3314],[3317-3318],[3320-3321],[3323-3324],[3327-3328],[3330-3331],[3333-3334],[3337-3338],[3340-3341],[3343-3344],[3347-3348],[3350-3351],[3353-3354],[3357-3358],[3360-3361],[3363-3364],[3367-3368],[3370-3371],[3373-3374],[3377-3378],[3380-3381],[3383-3384],[3387-3388],[3390-3391],[3393-3394],[3397-3398],[3400-3401],[3403-3404],[3407-3408],[3410-3411],[3413-3414],[3417-3418],[3420-3421],[3423-3424],[3427-3428],[3430-3431],[3433-3434],[3437-3438],[3440-3441],[3443-3444],[3447-3448],[3450-3451],[3453-3454],[3457-3458],[3460-3461],[3463-3464],[3467-3468],[3470-3471],[3473-3474],[3477-3478],[3480-3481],[3483-3484],[3487-3488],[3490-3491],[3493-3494],[3497-3498],[3500-3501],[3503-3504],[3507-3508],[3510-3511],[3513-3514],[3517-3518],[3520-3521],[3523-3524],[3527-3528],[3530-3531],[3533-3534],[3537-3538],[3540-3541],[3543-3544],[3547-3548],[3550-3551],[3553-3554],[3557-3558],[3560-3561],[3563-3564],[3567-3568],[3570-3571],[3573-3574],[3577-3578],[3580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Table 1. Continued.

3177	<i>Actinomycetes</i>	Dipeptidyl aminopeptidase IV inhibitor	29	AP	[123-129],[162-163],[264-265],[294-295],[369-370],[375-376],[393-394],[405-406],[456-457],[567-568],[606-607],[636-637],[669-670],[681-682],[684-685],[723-724],[744-745],[765-766],[816-817],[825-826],[912-913],[984-985],[990-991],[1014-1015],[1017-1018],[1020-1021],[1092-1093],[1411-1412],[1417-1418]
3178	<i>Actinomycetes</i>	Dipeptidyl aminopeptidase IV inhibitor	7	FP	[312-313],[378-379],[462-463],[549-550],[648-649],[843-844],[939-940]
3179	<i>Actinomycetes</i>	Dipeptidyl aminopeptidase IV inhibitor	34	PA	[150-151],[189-190],[249-250],[285-286],[306-307],[345-346],[351-352],[420-421],[429-430],[444-445],[450-451],[525-526],[534-535],[594-595],[603-604],[615-616],[639-640],[741-742],[756-757],[777-778],[810-811],[819-820],[867-868],[882-883],[891-892],[1008-1009],[1026-1027],[1038-1039],[1041-1042],[1047-1048],[1053-1054],[1104-1105],[1222-1223],[1312-1313]
3180	<i>Actinomycetes</i>	Dipeptidyl aminopeptidase IV inhibitor	16	LP	[96-97],[111-112],[156-157],[222-223],[228-229],[273-274],[447-448],[501-502],[612-613],[705-706],[861-862],[930-931],[942-943],[1125-1126],[1168-1169],[1405-1406]
3181	<i>Actinomycetes</i>	Dipeptidyl aminopeptidase IV inhibitor	2	VP	[144-145],[630-631]
3182	<i>Actinomycetes</i>	Dipeptidyl aminopeptidase IV inhibitor	2	LL	[1355-1356],[1356-1357]
3183	<i>Actinomycetes</i>	Dipeptidyl aminopeptidase IV inhibitor	1	VV	[927-928]
3201	Synthetic	Chymotrypsin inhibitor	1	GAW	[1388-1390]
3782	<i>Streptomyces</i>	Dipeptidyl-carboxypeptidase inhibitor	24	PPGP	[114-117],[117-120],[213-216],[300-303],[342-345],[426-429],[522-525],[588-591],[657-660],[738-741],[753-756],[774-777],[807-810],[852-855],[864-867],[894-897],[963-966],[1044-1047],[1086-1089],[1131-1134],[1146-1149],[1149-1152],[1152-1155],[1155-1158]
3744	Elastin	Chemotactic	1	VGAPG	[823-827]
3046	Synthetic	Anorectic-Inhibitor of insulin secretion	32	PGP	[97-99],[112-114],[115-117],[118-120],[145-147],[157-159],[163-165],[214-216],[247-249],[280-282],[301-303],[340-342],[343-345],[394-396],[418-420],[427-429],[442-444],[448-450],[514-516],[523-525],[532-534],[550-552],[568-570],[589-591],[613-615],[637-639],[658-660],[715-717],[739-741],[754-756],[772-774],[775-777],[808-810],[817-819],[826-828],[853-855],[862-864],[865-867],[889-891],[895-897],[916-918],[943-945],[964-966],[1021-1023],[1045-1047],[1087-1089],[1126-1128],[1132-1134],[1147-1149],[1150-1152],[1153-1155],[1156-1158]
3164	Laminin	Embryotoxic	3	RGD	[91-93],[712-714],[1060-1062]
4005	Synthetic	Activating ubiquitin-mediated proteolysis	2	RA	[1184-1185],[1367-1368]
4006	Synthetic	Activating ubiquitin-mediated proteolysis	2	LA	[972-973],[1410-1411]

¹β-LG – bovine β-lactoglobulin. ²β-CN – bovine β-casein. ³α₁-CN – bovine α₁-casein. ⁴BSA – bovine serum albumin. ⁵κ-CN – bovine κ-casein. ⁶α-LA – bovine α-lactalbumin.

antiamnestic, antithrombotic, and regulating ion flow. Bovine caseinomacropeptide – C-terminal fragment of κ-casein is one of the most known example of multifunctional bioactive peptide. It reveals e.g. activities such as antibacterial, antiviral, regulating action of digestive tract, and toxin binding (Dziuba and Minkiewicz, 1996).

As a qualitative parameter, the biological activity profile was not sufficient for the evaluation of proteins as precursors of biologically active peptides. Hence, use parameter *A* was used, permitting a quantitative determination of the trait analyzed, i.e., the value of protein as a source of biologically active peptides. The procedure of analysis of distributive series enabled to create five sub-families within each protein family. There are no explicit rules of handling the determination

of the span and number of sub-families (intervals). Usually, they are established by intuition so that the distributive series provides relatively clear distribution of a trait. In the present study, the simplest model of distributive series was applied, in which constant values of class intervals (five sub-families) and an equal span of the intervals were established for each of the analyzed sets (families of proteins, precursors of peptides with a given activity). The number of individual sub-families demonstrated a high diversity. In some cases, a given family was not represented by any of the proteins. This means that the intensity value of the trait examined (occurrence frequency of bioactive fragments (*A*) for all cases examined) did not fit to the defined class interval. The above situation occurred during the division of families with anticoagulant, antiamnesic, regulating ion

Table 2. The richest sub-families of proteins – precursors of peptides with selected activities.

Biological activity	BIOPEP ID	Protein	A parameter value
Antihypertensive	1097; 1199;	β -casein gen. var. A1; A2; A3; C; E bovine (<i>Bos taurus</i>)	0.224880
	1101; 1102		
	1100; 1103	β -casein gen. var. B; F, bovine (<i>Bos taurus</i>)	0.220096
Antithrombotic	1111	collagen α -1(III) chain, bovine (<i>Bos taurus</i>)	0.274238
	1112	collagen α -1(I) chain (fragment) bovine, (<i>Bos taurus</i>)	0.272144
	1113	collagen α -1(I) chain precursor, chicken (<i>Gallus gallus</i>)	0.212291
Antiamnestic	1111	collagen α -1(III) chain, bovine, (<i>Bos taurus</i>)	0.272392
	1112	collagen α -1(I) chain (fragment), bovine (<i>Bos taurus</i>)	0.267009
	1113	collagen α -1(I) chain precursor, chicken (<i>Gallus gallus</i>)	0.210196
Immunomodulating	1115	α -lactalbumin, bovine (<i>Bos taurus</i>)	0.024590
	1077; 1079;	α -lactalbumin, human (<i>Homo sapiens</i>); α -lactalbumin,	0.024390
	1082	goat (<i>Capra hircus</i>); α -lactalbumin, sheep (<i>Ovis aries</i>)	
	1098; 1102	β -casein gen. var. A2; E, bovine (<i>Bos taurus</i>)	0.023923
	1125	myoglobin, horse (<i>Equus caballus</i>)	0.022222
	1108	Flavodoxin mutant: D58P (<i>Clostridium beijerinckii</i>)	0.021429
	1154	Prolamin precursor (clone PPROL 14), rice (<i>Oryza sativa</i>)	0.020270
	1152	Prolamin precursor (clone PPROL 7), rice (<i>Oryza sativa</i>)	0.020134
	1155; 1169;	Prolamin precursor (clone PPROL 4A), rice (<i>Oryza sativa</i>);	0.020000
	1232	monellin chain B (II), serendipity berry (<i>Dioscoreophyllum</i>	
		cumminsii); pancreatic trypsin inhibitor (precursor),	
Antioxidative	1224	bovine aprotinin (<i>Bos taurus</i>)	0.047945
	1231; 1234	Hemoglobin β -chain, major-form, rat (<i>Rattus norvegicus</i>)	0.034247
		hemoglobin β -chain, horse (<i>Equus caballus</i>); hemoglobin	
Coeliac-toxic	1117	β -chain, human (<i>Homo sapiens</i>)	0.029586
	1177	κ -casein gen. var. A, bovine (<i>Bos taurus</i>)	0.041985
		α/β -gliadin precursor (prolamin) (class a-I),	
		wheat (<i>Triticum aestivum</i>)	
	1189	ω -gliadin fragment, wheat (<i>Triticum aestivum</i>)	0.035714
	1179	α/β -gliadin precursor (prolamin) (MM1),	0.029316
		wheat (<i>Triticum aestivum</i>)	
	1178	α/β -gliadin precursor (prolamin) (class a-II),	0.027491
		wheat (<i>Triticum aestivum</i>)	
	1180	α/β -gliadin precursor (prolamin) (class a-III),	0.024823
		wheat (<i>Triticum aestivum</i>)	
	1182	α/β -gliadin precursor (prolamin) (clone PW 1215),	0.020270
		wheat (<i>Triticum aestivum</i>)	
	1183	α/β -gliadin precursor (prolamin) (class a-IV),	0.020202
		wheat (<i>Triticum aestivum</i>)	
	1184	α/β -gliadin precursor (prolamin) (clone PW8142),	0.019169
		wheat (<i>Triticum aestivum</i>)	
	1181	α/β -gliadin precursor (prolamin) (class a-V),	0.018809
		wheat (<i>Triticum aestivum</i>)	
	1186	α/β -gliadin fragment (prolamin) (clone PTO A10),	0.005376
		wheat (<i>Triticum aestivum</i>)	
	1187	ω -gliadin precursor (fragment), wheat (<i>Triticum aestivum</i>)	0.003984
	1147; 1185	ω -gliadin precursor, wheat (<i>Triticum aestivum</i>);	0.003436
		ω -gliadin B precursor, wheat (<i>Triticum aestivum</i>)	
Inducing contractions of smooth muscles	1117	κ -casein gen. var. A, bovine (<i>Bos taurus</i>)	0.011834
	1109	κ -casein, goat (<i>Capra hircus</i>)	0.010417
Chemotactic	1107	Elastin precursor (tropoelastin) (<i>Bos taurus</i>)	0.023578
	1112	Collagen α -1(I) chain (fragment), bovine (<i>Bos taurus</i>)	0.001284
Embriotoxic	1192	PR-10 protein, white lupine (<i>Lupinus albus</i>)	0.006329
	1143	Legumin 11S globulin, ginkgo (<i>Ginkgo biloba</i>)	0.002273
	1113	Collagen α -1(I) chain precursor, chicken (<i>Gallus gallus</i>)	0.002095
	1076	Connectin fragment (titin), chicken (<i>Gallus gallus</i>)	0.001511
	1112	Collagen α -1(I) chain (fragment), bovine (<i>Bos taurus</i>)	0.001284
	1111	Collagen α -1(III) chain, bovine (<i>Bos taurus</i>)	0.000923
	1176	α -hordothionin precursor (purothionin II),	0.078740
Opioid		barley (<i>Hordeum vulgare</i>)	
	1080	α -lactalbumin, rabbit (<i>Oryctolagus cuniculus</i>)	0.081970
	1110	Wheat glutenin, high molecular weight subunit PW212 precursor	0.121359
		(<i>Triticum aestivum</i>)	

(Continued)

Table 2. Continued.

Biological activity	BIOPEP ID	Protein	A parameter value
Regulating ion flow	1191	Narbonin, vetch, (<i>Vicia pannonica</i>)	0.010309
	1190	Narbonin, narbon bean (<i>Vicia narbonensis</i>)	0.010345
	1126	Phycocyanin, blue-green bacteria, (<i>Cyanobacteria</i>)	0.012346
	117	Monellin chain A (I) serendipity berry (<i>Dioscoreophyllum cumminsii</i>)	0.022222
Regulating the functions of the gastric mucosa	1113	Collagen α -1(I) chain precursor, chicken (<i>Gallus gallus</i>)	0.210195
	1112	Collagen α -1(I) chain (fragment), bovine (<i>Bos taurus</i>)	0.267009
	1111	Collagen α -1(III) chain, bovine (<i>Bos taurus</i>)	0.272391
Dipeptidyl aminopeptidase IV inhibitors	1200	Epidermal retin acid binding protein EBP, mouse (<i>Arabidopsis thaliana</i>)	0.181818
	1113	Collagen α -1(I) chain precursor, chicken (<i>Gallus gallus</i>)	0.204609
	1112	Collagen α -1(I) chain (fragment), bovine (<i>Bos taurus</i>)	0.258023
Activating ubiquitin-mediated proteolysis,	1149	Kafirin PGK1 precursor, sorghum (<i>Sorghum vulgare</i>)	0.033457
	1197	Kafirin PSK8 precursor, sorghum bicolor (<i>Sorghum vulgare</i>)	0.037453
	1091	Lysozyme C precursor, human (<i>Homo sapiens</i>)	0.038462
	1196	Kafirin PSKR2 precursor, sorghum bicolor (<i>Sorghum vulgare</i>)	0.041199
Regulating the action mechanism of phosphoinositol	1118	Connectin (titin), fragment, chicken (<i>Gallus gallus</i>)	0.046154
	1077;	α -lactalbumin, human (<i>Homo sapiens</i>); α -lactalbumin, horse (<i>Equus caballus</i>); α -lactalbumin, goat (<i>Capra hircus</i>); α -lactalbumin, sheep (<i>Ovis aries</i>); α -Lactalbumin, guinea pig (<i>Cavia porcellus</i>); α -lactalbumin, arabian camel (<i>Camelus dromedarius</i>)	0.008130
	1079;1082;		
	1083; 1085		
Neuropeptide inhibitors	1115	α -lactalbumin, bovine (<i>Bos taurus</i>)	0.008197
	1081	α -lactalbumin, red-necked wallaby (<i>Macropus rufogriseus</i>)	0.008264
	1093	Lysozyme precursor, silk moth (<i>Bombyx mori</i>)	0.008333
	1195	major urinary protein 1 precursor, mouse (<i>Mus musculus</i>)	0.009259
Ligands of bacterial permease	1110	Wheat glutenin, high molecular weight subunit PW212 precursor (<i>Triticum aestivum</i>)	0.162621
	1125	Myoglobin, horse (<i>Equus caballus</i>)	0.037037
Stimulating the synthesis of red blood cells	1138	Troponin C, bovine (<i>Bos taurus</i>)	0.052000
	1214	Hemoglobin α -chains, horse (<i>Equus caballus</i>)	0.007062
Hemolytic Anorectic	1217	Hemoglobin α -chain, pig (<i>Sus scrofa</i>)	0.007092
	1090	α -S ₂ -casein gen. var. A, bovine (<i>Bos taurus</i>)	0.024155
	1107	Elastin precursor (tropoelastin), bovine (<i>Bos taurus</i>)	0.001387
	1143	Legumin 11S globulin, ginkgo (<i>Ginkgo biloba</i>)	0.002273
Opioid-antagonistic	1097; 1103	β -casein gen. var. A1; A2; A3; B; C; E; F, bovine (<i>Bos taurus</i>)	0.004785
	1113	Collagen α -1(I) chain precursor, chicken (<i>Gallus gallus</i>)	0.036313
	1111	Collagen α -1(III) chain, bovine (<i>Bos taurus</i>)	0.041551
	1112	Collagen α -1(I) chain (fragment), bovine (<i>Bos taurus</i>)	0.044929
Binding and transporting metals and metal ions	1087; 1089	α -S ₁ -casein gen. var. B; C; D, bovine (<i>Bos taurus</i>)	0.005025
	1086	α -S ₁ -casein gen. var. A, bovine (<i>Bos taurus</i>)	0.005376
	1109	κ -casein, goat (<i>Capra hircus</i>)	0.010417
	1117	κ -casein gen. var. A, bovine (<i>Bos taurus</i>)	0.011834
Antibacterial and antiviral	1236	Lactoferrin precursor, bovine (<i>Bos taurus</i>)	0.005650
	1212	Lactoferrin, bovine (<i>Bos taurus</i>)	0.005806
	1090	α -S ₂ -casein gen. var. A, bovine (<i>Bos taurus</i>)	0.024155
	1121	Lactoferrin, human (<i>Homo sapiens</i>)	0.004335
	1213	Lactoferrin, goat (<i>Capra hircus</i>)	0.005805
	1233	Hemoglobin α -chain, bovine (<i>Bos taurus</i>)	0.007092
	1084	α -lactalbumin, rat (<i>Rattus norvegicus</i>)	0.007143
	1085	α -lactalbumin, arabian camel (<i>Camelus dromedarius</i>)	0.008130
	1212	Lactoferrin, bovine (<i>Bos taurus</i>)	0.015965
	1236	Lactoferrin precursor, bovine (<i>Bos taurus</i>)	0.016949
	1090	α -S ₂ -casein gen. var. A, bovine (<i>Bos taurus</i>)	0.019324
	1115	α -lactalbumin, bovine (<i>Bos taurus</i>)	0.024590
	1082	α -lactalbumin, sheep (<i>Ovis aries</i>)	0.032520

flow, regulating the functions of the gastric mucosa, and neuropeptide inhibitor activities. In the case of the families of peptide precursors with toxic, smooth-muscle contraction inducing, chemotactic, embryotoxic, stimulating the synthesis of red blood cells, hemolytic, anorectic, opioid-antagonistic, binding and transporting metals and metal ions, as well as antibacterial and antiviral activities, no sub-families were created due to their low number. The largest families were composed of proteins — precursors of antihypertensive peptides and dipeptidyl aminopeptidase IV inhibitors, as well as those activating ubiquitin-mediated proteolysis and opioid ones whereas the smallest one by proteins — of precursors of hemolytic and chemotactic peptides, peptides binding and transporting metals and metal ions, stimulating red blood cells synthesis, inducing contractions of smooth muscles (Table 2).

Amongst representatives of the largest protein sub-families proteins of wheat α - and β -gliadins, caseins, and collagen, dominated. Proteins being a source of peptides with antihypertensive, antithrombotic, antiamnesic, regulating the functions of the gastric mucosa, and dipeptidyl aminopeptidase IV inhibitor activities were characterized by the highest values of parameter A . In some cases the value of discriminant A was equal to zero (results not shown). It does not mean that 'A-zero-proteins' are the bad source of bioactive peptides but implies that they can be a better source of peptides with other kinds of activity. Taking into account all analyzed protein sequences from the BIOPEP database, it was found that the highest relative values of discriminant A were characteristic of bovine collagen α -1(III) chain and concerned antithrombotic, antiamnesic, and regulating the functions of gastric mucosa activities. The values were 0.274238, 0.272392, and 0.272391, respectively. High frequency occurrence of fragments with antithrombotic, antiamnesic, and regulating the functions of gastric mucosa activities (A) for bovine collagen can suggest that collagen, apart from its basic function as a connective tissue, can also be the precursor of endogenous bioactive peptides. This is consistent with the hypothesis proposed by Karelin et al. (1998), according to which all proteins present in an organism can play the role of peptide reserves regulating its functions. The relatively high values of parameter A were obtained for antihypertensive activity of bovine β -casein (β -CN) genetic variants ($A=0.22488$ for β -CN A1; A2; A3; C; E and $A=0.220096$ for β -CN B; F). Low value of discriminant A dissimilarity indicate that mutations concerning changes in single amino acid residues cause only small changes in the occurrence frequency of antihypertensive activity and potential biological activity of these proteins. The presence of β -CN-originated peptides was also confirmed experimentally by Meisel (1998).

The classification of food proteins into sub-families with exposure of sub-families, the richest potential

precursors of bioactive peptides, is an excellent source of information for technologists. The proposed division can be a measure of protein selection applied in nutraceutical production (i.e., physiologically active functional food compounds — food with specific therapeutic properties). In addition, such a division can be highly useful while designing proteolysis processes aimed at obtaining bioactive peptides from precursor protein. Our previous investigations (Dziuba et al., 1999a, 1999b, 2002) demonstrated that the richer the peptide profile of protein in bioactive fragments, the higher the likelihood of those fragments released by proteolytic enzymes. Design of the proteolysis process of proteins, the richest precursors of bioactive peptides, will be the subject of our further studies. The results presented herein are a contribution to a rapidly-developing, new branch of food science focused on obtaining tasty and safe food products lowering the risk of falling ill, in accordance with the ancient Chinese's motto: 'Medicine and food are isogenic.'

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REFERENCES

- Brody E. (2000). Biological activities of bovine glycomacropeptide. *British Journal of Nutrition* 84(Suppl 1): S39-S46.
- Bush R.K. and Hefle S.L. (1996). Food allergens. *Critical Reviews in Food Science and Nutrition* 36: 119-163.
- Campbell-Platt G. (1994). Fermented foods — a world perspective. *Food Research International* 27: 253-257.
- Darewicz M., Dziuba J. and Dziuba M. (2006). Functional properties and biological activities of bovine casein proteins and peptides. *Polish Journal of Food and Nutrition Sciences* 15/56: 79-86.
- De Felice S.L. (1995). The nutraceutical revolution: its impact on food industry R and D. *Trends in Food Science and Technology* 6: 59-61.
- Dziuba J., Minkiewicz P. and Puszka K. (1995). Wheat gliadins as potential precursors of bioactive peptides. *Acta Academiae Agriculturae ac Technicae Olstenensis* 28: 3-16.
- Dziuba J. and Minkiewicz P. (1996). Influence of glycosylation on micelle-stabilizing ability and biological properties of C-terminal fragments of cow's κ -casein. *International Dairy Journal* 6: 1017-1044.
- Dziuba J., Minkiewicz P. and Nałęcz D. (1999a). Biologically active peptides from plant and animal proteins. *Polish Journal of Food and Nutrition Sciences* 8/49(1): 3-16.
- Dziuba J., Minkiewicz P., Nałęcz D. and Iwaniak A. (1999b). Database of biologically active peptide sequences. *Nahrung* 43/3: 190-195.
- Dziuba J., Iwaniak A., Darewicz M. and Niklewicz M. (2002). Computer simulation of animal proteins proteolysis in the aspect of bioactive peptides obtaining. *Polish Journal of Natural Sciences* 10(1): 209-222.
- Dziuba J., Iwaniak A. and Niklewicz M. (2003). Database of protein and bioactive peptide sequences — BIOPEP. Available at <http://www.uwm.edu.pl/biochemia>, accessed 3 July 2007.

- Dziuba J., Niklewicz M., Iwaniak A. and Darewicz M. (2004). Bioinformatic-aided prediction for release possibilities of bioactive peptides from plant proteins. *Acta Alimentaria* 33: 227–235.
- Dziuba J., Niklewicz M., Iwaniak A., Darewicz M. and Minkiewicz P. (2005). Structural properties of bioactive animal protein fragments accessible for proteolytic enzymes. *Polimery* 6: 424–429.
- Dziuba J. and Iwaniak A. (2006). Database of protein and bioactive peptide sequences. In: Mine Y. and Shahidi F. (eds). *Nutraceutical Proteins and Peptides in Health and Disease*. London: CRC-Taylor and Francis. pp. 543–563.
- Friedman M. (1996). Nutritional value of proteins from different food sources. A review. *Journal of Agricultural and Food Chemistry* 44: 6–29.
- Fujita H., Sasaki R. and Yoshikawa M. (1995). Purification and the antihypertensive activity of orally administered ovokinin, a vasorelaxing peptide derived from ovalbumin by emulsification in egg phosphatidylcholine. *Bioscience, Biotechnology and Biochemistry* 59: 2344–2345.
- Fukumoto S. and Yoshikawa M. (1992). Opioid peptides from wheat gluten: their isolation and characterisation. *FEBS Letters* 296: 107–111.
- Gibbs B.F., Zougman A., Masse R. and Mulligan C. (2004). Production and characterization of bioactive peptides from soy hydrolysate and soy-fermented food. *Food Research International* 37: 123–131.
- Gobbetti M., Stepaniak L., De Angelis M., Corsetti A. and Di Cagno R. (2002). Latent Bioactive Peptides in Milk Proteins: Proteolytic Activation and Significance in Dairy. *Critical Reviews in Food Sciences and Nutrition* 42: 223–239.
- Grimble G.K. (1994). The significance of peptides in clinical nutrition. *Annual Review of Nutrition* 14: 419–448.
- Hartmann R. and Meisel H. (2002). Cytochemical assessment of phosphopeptides derived from casein as potential ingredients for functional food. *Nahrung* 46: 427–431.
- Hilliam M. (2003). Future for dairy products and ingredients in the functional food market. *Australian Journal of Dairy Technology* 58: 98–103.
- Karabin A.A., Blishchenko E.Y. and Ivanov V.T. (1998). A novel system of peptidergic regulation. *FEBS Letters* 428: 7–12.
- Kilara A. and Panyam D. (2003). Peptides From Milk Proteins and Their Properties. *Critical Reviews in Food Science and Nutrition* 43: 607–633.
- Korhonen H., Pihlanto-Leppälä A., Rantamäki P. and Tupasela T. (1998). Impact of processing on bioactive proteins and peptides. *Trends in Food Science and Technology* 9: 307–319.
- Korhonen H. and Pihlanto A. (2003). Bioactive peptides: new challenges and opportunities for the dairy industry. *Australian Journal of Dairy Technology* 58: 129–134.
- Lane D. (2003). Stem and leaf displays. Available at <http://cnx.org/content/m10157/latest>, accessed 3 July 2007.
- Latham P.W. (1999). Therapeutic peptides revisited. *Nature Biotechnology* 17: 755–758.
- Maruyama S., Nonaka I. and Tanaka H. (1993). Inhibitory effects of enzymatic hydrolysates of collagen and collagen-related synthetic peptides on fibrinogen-thrombin clotting. *Biochimica et Biophysica Acta* 1164: 215–218.
- Meisel H. (1998). Overview on milk protein-derived peptides. *International Dairy Journal* 8: 363–373.
- Meisel H. (2001). Bioactive peptides from milk proteins: a perspective for consumers and producers. *Australian Journal of Dairy Technology* 56(2): 83–92.
- Meisel H. and Bockelmann W. (1999). Bioactive peptides encrypted in milk proteins: proteolytic activation and thropho-functional properties. *Antonie van Leeuwenhoek* 76: 207–215.
- Pihlanto-Leppälä A., Rokka A. and Korhonen H. (1998). Angiotensin I converting enzyme inhibitory peptides derived from bovine milk proteins. *International Dairy Journal* 8: 325–331.
- Pihlanto-Leppälä A. (2001). Bioactive peptides derived from bovine whey proteins: opioid and ace-inhibitory peptides. *Trends in Food Science and Technology* 11: 347–356.
- Rutherford-Markwick K.W.J. and Moughan P.J. (2005). Bioactive peptides derived from food. *Journal of AOAC International* 88: 955–966.
- Schlimme E. and Meisel H. (1995). Bioactive peptides derived from milk proteins. Structural, physiological and analytical aspects. *Nahrung* 39: 1–20.
- Schmidl M.K., Taylor S. and Nordlee J.A. (1994). Use of hydrolysate-based products in special medical diets. *Food Technology* 48: 77–85.
- Shah N. (2000). Effects of milk-derived bioactives: an overview. *British Journal of Nutrition* 84(Suppl 1): S3–S10.
- Silva S.V. and Malcata F.X. (2005). Caseins as a source of bioactive peptides. *International Dairy Journal* 15: 1–15.
- Vermeirssen V., Van Camp J. and Verstraete W. (2004). Bioavailability of angiotensin I-converting enzyme inhibitory peptides. *British Journal of Nutrition* 92: 357–366.
- Yoshikawa M., Fujita H., Matoba N., Takenaka Y., Yamamoto T., Yamauchi R., Tsuruki H. and Takahata K. (2000). Bioactive peptides derived from food proteins preventing lifestyle-related diseases. *BioFactors* 12: 143–146.