

Supplement

In Silico Analysis of Individual Fractions of Bovine Casein as Precursors of Bioactive Peptides—Influence of Post-Translational Modifications

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Table S1. Protein sequences used for analyses. Post-translation modifications are indicated using red font.

Name ¹	ID in BIOPEP-UWM protein database ²	Access. No. in UniProt database	Amino acid sequence with consideration of modifications of amino acid residues ^{3; 4}
α_{s1} -casein A	1834	P02662	RPKHPIKHQGLPQPFPEVFGKEKVNELSKDIG<S[3*]>E<S[3*]>TEDQAMEDIKQMEAE<S[3*]>I<S[3*]><S[3*]><S[3*]>EEIVPN<S[3*]>VEQKHIQKEDVPSERYLGYLEQLRLKKYKVPQLEIVPN<S[3*]>AEERLHSMKEGIHAQQKEPMIGVNQELAYFYPELFRQFYQLDAYPSGAWYYVPLGTQYTDAPSFSDIPNPIGSENSEKTTMPLW
α_{s1} -casein B	1835	P02662	RPKHPIKHQGLPQEVNENLLRFFVAPFPEVFGKEKVNELSKDIG<S[3*]>E<S[3*]>TEDQAMEDIKQMEAE<S[3*]>I<S[3*]><S[3*]><S[3*]>EEIVPN<S[3*]>VEQKHIQKEDVPSERYLGYLEQLRLKKYKVPQLEIVPN<S[3*]>AEERLHSMKEGIHAQQKEPMIGVNQELAYFYPELFRQFYQLDAYPSGAWYYVPLGTQYTDAPSFSDIPNPIGSENSEKTTMPLW
α_{s1} -casein C	1836	P02662	RPKHPIKHQGLPQEVNENLLRFFVAPFPEVFGKEKVNELSKDIG<S[3*]>E<S[3*]>TEDQAMEDIKQMEAE<S[3*]>I<S[3*]><S[3*]><S[3*]>EEIVPN<S[3*]>VEQKHIQKEDVPSERYLGYLEQLRLKKYKVPQLEIVPN<S[3*]>AEERLHSMKEGIHAQQKEPMIGVNQELAYFYPELFRQFYQLDAYPSGAWYYVPLGTQYTDAPSFSDIPNPIGSENSGKTTMPLW
α_{s1} -casein D	1837	P02662	RPKHPIKHQGLPQEVNENLLRFFVAPFPEVFGKEKVNELSKDIG<S[3*]>E<S[3*]>TEDQ<T[3*]>MEDIKQMEAE<S[3*]>I<S[3*]><S[3*]><S[3*]>EEIVPN<S[3*]>VEQKHIQKEDVPSERYLGYLEQLRLKKYKVPQLEIVPN<S[3*]>AEERLHSMKEGIHAQQKEPMIGVNQELAYFYPELFRQFYQLDAYPSGAWYYVPLGTQYTDAPSFSDIPNPIGSENSEKTTMPLW

α_{s2} -casein A	1838	P02663	KNTMEHV<S[3*]><S[3*]><S[3*]>EE<S[3*]>IISQETYKQEKMAINP<S[3*]>KENL<C>STF<C>KEVVRNANEEYSIG<S[3*]><S[3*]><S[3*]>EE<S[3*]>AEVATEEVKITVDDKHYQKALNEINQFYQKFPQYLQYLYQGPIVLNPWDQVKRNAVPITPTLNREQLSTSEENSKKTVDM<S[3*]>TEVFTKKTKLTEEEKNRLNFLKKISQRYQKFALPQYLKTVYQHQKAMKPWIQPKTKVIPYVRYL
α_{s2} -casein B	1839	P02663	KNTMEHVF<S[3*]><S[3*]>EE<S[3*]>IISQETYKQEKMAINP<S[3*]>KENL<C>STF<C>KEVVRNANEEYSIG<S[3*]><S[3*]><S[3*]>EE<S[3*]>AEVATEEVKITVDDKHYQKALNEINQFYQKFPQYLQYLYQGPIVLNPWDQVKRNAVPITPTLNREQLSTSEENSKKTVDM<S[3*]>TEVFTKKTKLTEEEKNRLNFLKKISQRYQKFALPQYLKTVYQHQKAMKPWIQPKTKVIPYVRYL
α_{s2} -casein C	1840	P02663	KNTMEHV<S[3*]><S[3*]><S[3*]>EE<S[3*]>IISQETYKQEKMAINP<S[3*]>KGNL<C>STF<C>KEVVRNTNEEYSIG<S[3*]><S[3*]><S[3*]>EE<S[3*]>AEVATEEVKITVDDKHYQKALNEINQFYQKFPQYLQYLYQGPIVLNPWDQVKRNAVPITPTLNREQLSISEENSKKTVDM<S[3*]>TEVFTKKTKLTEEEKNRLNFLKKISQRYQKFALPQYLKTVYQHQKAMKPWIQPKTKVIPYVRYL
α_{s2} -casein D	1841	P02663	KNTMEHV<S[3*]><S[3*]><S[3*]>EE<S[3*]>IISQETYKQEKMAINP<S[3*]>KENL<C>STF<C>KEVVRNANEE<S[3*]>AEVATEEVKITVDDKHYQKALNEINQFYQKFPQYLQYLYQGPIVLNPWDQVKRNAVPITPTLNREQLSTSEENSKKTVDM<S[3*]>TEVFTKKTKLTEEEKNRLNFLKKISQRYQKFALPQYLKTVYQHQKAMKPWIQPKTKVIPYVRYL
β -casein A1	1842	P02666	RELEELNVPGEIVE<S[3*]>L<S[3*]><S[3*]><S[3*]>EESITRINKKIEKFQ<S[3*]>EEQQQTEDELQDKIHFAQTQSLVYPPGPIHNSLPQNIPPLTQTPVVVPPFLQPEVMGVSKVKEAMAPKHKEMPFPKYPVPFTESQSLTLTDVENLHLPPLLQSWMHQPHQPLPPTVMFPPQSVLSLSQSKVLPVPEKAVPYPQRDMPIQAFLLYQEPVLGPVRGPFPIIV
β -casein A2	1843	P02666	RELEELNVPGEIVE<S[3*]>L<S[3*]><S[3*]><S[3*]>EESITRINKKIEKFQ<S[3*]>EEQQQTEDELQDKIHFAQTQSLVYPPGPIHNSLPQNIPPLTQTPVVVPPFLQPEVMGVSKVKEAMAPKHKEMPFPKYPVEPFTEQSLLTLTDVENLHLPPLLQSWMHQPHQPLPPTVMFPPQSVLSLSQSKVLPVPQKAVPYPQRDMPIQAFLLYQEPVLGPVRGPFPIIV
β -casein A3	1844	P02666	RELEELNVPGEIVE<S[3*]>L<S[3*]><S[3*]><S[3*]>EESITRINKKIEKFQ<S[3*]>EEQQQTEDELQDKIHFAQTQSLVYPPGPIHNSLPQNIPPLTQTPVVVPPFLQPEVMGVSKVKEAMAPKQKEMPFPKYPVEPFTEQSLLTLTDVENLHLPPLLQSWMHQPHQPLPPTVMFPPQSVLSLSQSKVLPVPQKAVPYPQRDMPIQAFLLYQEPVLGPVRGPFPIIV
β -casein B	1845	P02666	RELEELNVPGEIVE<S[3*]>L<S[3*]><S[3*]><S[3*]>EESITRINKKIEKFQ<S[3*]>EEQQQTEDELQDKIHFAQTQSLVYPPGPIHNSLPQNIPPLTQTPVVVPPFLQPEVMGVSKVKEAMAPKHKEMPFPKYPVEPFTERQSLTLTDVENLHLPPLLQSWMHQPHQPLPPTVMFPPQSVLSLSQSKVLPVPQKAVPYPQRDMPIQAFLLYQEPVLGPVRGPFPIIV

κ-casein A	1846	P02668	<P[40]>EQNQEQPIR<C>EKDERFFSDKIAKYIPIQYVLSRPSYGLNY YQQKPVALINNQFLPYPHYAKPAAVRSPAQILQWQVLSNTVPAKS<C> QAQPTTMARHHPHLSFMAIPPKKNQDKTEIPTINTIA<S[3*]>GEPTST PTTEAVESTVATLEDSPEVIESPPEINTVQVTSTAV
κ-casein B	1847	P02668	<P[40]>EQNQEQPIR<C>EKDERFFSDKIAKYIPIQYVLSRPSYGLNY YQQKPVALINNQFLPYPHYAKPAAVRSPAQILQWQVLSNTVPAKS<C> QAQPTTMARHHPHLSFMAIPPKKNQDKTEIPTINTIA<S[3*]>GEPTS TPTIEAVESTVATLEASPEVIESPPEINTVQVTSTAV
κ-casein B2	1849	P02668	<P[40]>EQNQEQPIR<C>EKDERFFSDKIAKYIPIQYVLSRPSYGLNY YQQKPVALINNQFLPYPHYAKPAAVRSPAQILQWQVLSNTVPAKS<C> QAQPTTMARHHPHLSFMAIPPKKNQDKTEIPTINTIA<S[3*]>GEPTS TPTIEAVESTVATLEASPEVTESPEINTVQVTSTAV
κ-casein C	1850	P02668	<P[40]>EQNQEQPIR<C>EKDERFFSDKIAKYIPIQYVLSRPSYGLNY YQQKPVALINNQFLPYPHYAKPAAVRSPAQILQWQVLSNTVPAKS<C> QAQPTTMAHHPHLSFMAIPPKKNQDKTEIPTINTIA<S[3*]>GEPTS TPTTEAVESTVATLEDSPEVIEGPPEINTVQVTSTAV

1. Capital letters denote genetic variants of individual casein fractions
2. BIOPEP-UWM protein database
3. Symbols of post-translation modifications are provided in Table 1 in main text.
4. Sequences do not contain signal peptides.

Table S2. Frequency of occurrence of bioactive fragments A and A₀ in individual genetic variants of α_{s1} -casein. Differences between sequences with and without post-translational modifications were indicated in red.

α_{s1} -CN	Variant A		Variant B		Variant C		Variant D	
Activity	A	A ₀	A	A ₀	A	A ₀	A	A ₀
ACE (EC 3.4.15.1) inhibitors	0.6237	0.6398	0.6382	0.6533	0.6432	0.6583	0.6382	0.6533
activating ubiquitin-dependent proteolysis	0.0054	0.0054	0.005	0.005	0.005	0.005	0.005	0.005
α -glucosidase (EC 3.2.1.20) inhibitors	0.0376	0.0376	0.0402	0.0402	0.0402	0.0402	0.0402	0.0402
antiamnestic (proline oligopeptidase - EC 3.4.21.26 inhibitors)	0.0161	0.0161	0.0151	0.0151	0.0151	0.0151	0.0151	0.0151
antibacterial	0.0161	0.0161	0.0352	0.0352	0.0302	0.0302	0.0352	0.0352
anticancer	0.0108	0.0108	0.0302	0.0302	0.0302	0.0302	0.0302	0.0302
antidiabetic	0.0054	0.0054	0.005	0.005	0.005	0.005	0.005	0.005
antifungal	0.0054	0.0054	0.005	0.005	0.005	0.005	0.005	0.005
antioxidative	0.2366	0.2366	0.2362	0.2362	0.2312	0.2312	0.2362	0.2362
antiviral	0	0	0.005	0.005	0.005	0.005	0.005	0.005
bacterial permease ligands	0.0054	0.0054	0.005	0.005	0.005	0.005	0.005	0.005
DPPIII (EC 3.4.14.4) inhibitors	0.0914	0.0914	0.0955	0.0955	0.0955	0.0955	0.0955	0.0955
DPPIV (EC 3.4.14.5) inhibitors	0.5914	0.6129	0.603	0.6231	0.598	0.6181	0.598	0.6281
antihypertensive	0.0054	0.0054	0.005	0.005	0.005	0.005	0.005	0.005
immunomodulating	0.0054	0.0054	0.0101	0.0101	0.0101	0.0101	0.0101	0.0101
immunostimulating	0.0108	0.0108	0.0101	0.0101	0.0101	0.0101	0.0101	0.0101
inhibitors	0.0054	0.0054	0.005	0.005	0.005	0.005	0.005	0.005
neuropeptides	0.0161	0.0161	0.0151	0.0151	0.0151	0.0151	0.0151	0.0151
opioid	0.0161	0.0161	0.0151	0.0151	0.0151	0.0151	0.0151	0.0151
opioid agonists	0.0054	0.0054	0.005	0.005	0.005	0.005	0.005	0.005
osteoanabolic	0.0054	0.0054	0.005	0.005	0.005	0.005	0.005	0.005
regulating	0.0054	0.0054	0.005	0.005	0.005	0.005	0.005	0.005
renin (EC 3.4.23.1) inhibitors	0.0215	0.0215	0.0251	0.0251	0.0251	0.0251	0.0251	0.0251

stimulating	0.0484	0.0645	0.0553	0.0704	0.0503	0.0653	0.0553	0.0704
All activities	1.7906	1.8443	1.8744	1.9247	1.8594	1.9096	1.8694	1.9297
<i>Percentage of activities with false-positive results [%]</i>	13.04		12.50		12.50		12.50	

Table S3. Frequency of occurrence of bioactive fragments A and A₀ in individual genetic variants of α_{s2} -casein. Differences between sequences with and without post-translational modifications were indicated in red.

α_{s2} -CN	Variant A		Variant B		Variant C		Variant D	
Activity	A	A ₀	A	A ₀	A	A ₀	A	A ₀
ACE (EC 3.4.15.1) inhibitors	0.4976	0.5121	0.5024	0.5169	0.4928	0.5072	0.5101	0.5202
anti inflammatory	0.0097	0.0097	0.0097	0.0097	0.0097	0.0097	0.0101	0.0101
antiamnestic (proline oligopeptidase - EC 3.4.21.26 inhibitors)	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0051	0.0051
antibacterial	0.058	0.058	0.058	0.058	0.058	0.058	0.0606	0.0606
antidiabetic	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0051	0.0051
antioxidative	0.1449	0.1498	0.1449	0.1498	0.1449	0.1498	0.1515	0.1566
antithrombotic	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0051	0.0051
bacterial permease ligands	0.0145	0.0145	0.0145	0.0145	0.0145	0.0145	0.0152	0.0152
binding	0.0097	0.0097	0.0097	0.0097	0.0097	0.0097	0.0101	0.0101
CaMPDE (EC 3.1.4.17) inhibitors	0.0338	0.0338	0.0338	0.0338	0.0338	0.0338	0.0354	0.0354
DPPIII (EC 3.4.14.4) inhibitors	0.0531	0.0531	0.0531	0.0531	0.0531	0.0531	0.0556	0.0556
DPPIV (EC 3.4.14.5) inhibitors	0.6812	0.715	0.686	0.715	0.686	0.7198	0.697	0.7323
hemolytic	0.0242	0.0242	0.0242	0.0242	0.0242	0.0242	0.0253	0.0253
immunomodulating	0	0.0048	0	0	0	0.0048	0	0.0051
neuropeptides	0.0193	0.0193	0.0193	0.0193	0.0193	0.0193	0.0202	0.0202
osteoanabolic	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0051	0.0051
regulating	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0051	0.0051
renin (EC 3.4.23.1) inhibitors	0.0386	0.0386	0.0386	0.0386	0.0386	0.0386	0.0404	0.0404
stimulating	0.0676	0.087	0.0676	0.0821	0.0676	0.087	0.0657	0.0758
All activities	1.6762	1.7536	1.6858	1.7487	1.6762	1.7535	1.7227	1.7884
Percentage of activities with false-positive results [%]	26.32		22.22		26.32		26.32	

Table S4. Frequency of occurrence of bioactive fragments A and A₀ in individual genetic variants of β -casein. Differences between sequences with and without post-translational modifications were indicated in red.

β -CN	Variant A1		Variant A2		Variant A3		Variant B	
Activity	A	A ₀	A	A ₀	A	A ₀	A	A ₀
α -amylase (EC 3.2.1.1) inhibitors	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
ACE (EC 3.4.15.1) inhibitors	0.7416	0.7416	0.823	0.823	0.823	0.823	0.7895	0.7895
AChE (EC 3.1.1.7) inhibitors	0.0096	0.0096	0.0096	0.0096	0.0096	0.0096	0.0096	0.0096
α -glucosidase (EC 3.2.1.20) inhibitors	0.067	0.067	0.0622	0.0622	0.0622	0.0622	0.0622	0.0622
anti inflammatory	0.0144	0.0144	0.0144	0.0144	0.0144	0.0144	0.0144	0.0144
anti-apoptotic	0	0	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
antiamnestic (proline oligopeptidase - EC 3.4.21.26 inhibitors)	0.0574	0.0574	0.0526	0.0526	0.0526	0.0526	0.0574	0.0574
antibacterial	0.0048	0.0048	0.0096	0.0096	0.0096	0.0096	0.0096	0.0096
anticancer	0.0144	0.0144	0.0335	0.0335	0.0335	0.0335	0.0287	0.0287
antidiabetic	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
antioxidative	0.11	0.11	0.1483	0.1483	0.1435	0.1435	0.1388	0.1388
antithrombotic	0.0287	0.0287	0.0287	0.0287	0.0287	0.0287	0.0287	0.0287
bacterial permease ligands	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
BChE (EC 3.1.1.8) inhibitors	0.0096	0.0096	0.0096	0.0096	0.0096	0.0096	0.0096	0.0096
binding	0.0191	0.0239	0.0239	0.0287	0.0191	0.0239	0.0239	0.0287
CaMPDE (EC 3.1.4.17) inhibitors	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
chemotactic	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
DPPIII (EC 3.4.14.4) inhibitors	0.0957	0.0957	0.0861	0.0861	0.0813	0.0813	0.0909	0.0909
DPPIV (EC 3.4.14.5) inhibitors	0.8134	0.8278	0.8469	0.8612	0.8421	0.8565	0.8278	0.8421
antihypertensive	0	0	0.0096	0.0096	0.0096	0.0096	0.0096	0.0096

immunomodulating	0.0144	0.0191	0.0191	0.0239	0.0191	0.0239	0.0144	0.0191
immunostimulating	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
inhibitors	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
lipoygenase inhibitors	0.0096	0.0096	0.0144	0.0144	0.0144	0.0144	0.0144	0.0144
neuropeptides	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
opioid	0.0096	0.0096	0.0191	0.0191	0.0191	0.0191	0.0144	0.0144
opioid agonists	0.0096	0.0096	0.0144	0.0144	0.0144	0.0144	0.0096	0.0096
osteoanabolic	0	0	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
regulating	0.0478	0.0526	0.0478	0.0526	0.0478	0.0526	0.0478	0.0526
renin (EC 3.4.23.1) inhibitors	0.0144	0.0144	0.0239	0.0239	0.0239	0.0239	0.0239	0.0239
stimulating	0.0766	0.0909	0.0861	0.1005	0.0766	0.0909	0.0766	0.0909
All activities	2.2061	2.2491	2.4308	2.4739	2.4021	2.4452	2.3498	2.3927
Percentage of activities with false-positive results [%]	17.86		16.13		16.13		16.13	

Table S5. Frequency of occurrence of bioactive fragments A and A₀ in individual genetic variants of κ -casein. Differences between sequences with and without post-translational modifications were indicated in red.

κ -CN	Variant A		Variant B		Variant B2		Variant C	
Activity	A	A ₀	A	A ₀	A	A ₀	A	A ₀
α -amylase (EC 3.2.1.1) inhibitors	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059
ACE (EC 3.4.15.1) inhibitors	0.5917	0.5976	0.5976	0.6036	0.5976	0.6036	0.5917	0.5917
α -glucosidase (EC 3.2.1.20) inhibitors	0.0592	0.0592	0.0651	0.0651	0.0651	0.0651	0.0592	0.0592
anti inflammatory	0.0178	0.0178	0.0178	0.0178	0.0178	0.0178	0.0178	0.0178
antiamnestic (proline oligopeptidase - EC 3.4.21.26 inhibitors	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0118	0.0059
antibacterial	0.0651	0.071	0.0592	0.0592	0.0592	0.0592	0.0592	0.0651
antioxidative	0.1775	0.1953	0.1775	0.1953	0.1716	0.1893	0.1834	0.1775
antithrombotic	0.0414	0.0414	0.0414	0.0414	0.0414	0.0414	0.0473	0.0414
antiviral	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059
bacterial permease ligands	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059
binding	0.0059	0.0059	0.0059	0.0059	0	0	0	0.0059
CaMPDE (EC 3.1.4.17) inhibitors	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059
contracting	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237
DPPIII (EC 3.4.14.4) inhibitors	0.0769	0.0769	0.0769	0.0769	0.0769	0.0769	0.0769	0.0769
DPPIV (EC 3.4.14.5) inhibitors	0.7633	0.7751	0.7633	0.7751	0.7692	0.7811	0.7692	0.7633
HMG-CoA reductase (EC 1.1.1.34) inhibitors	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059
antihypertensive	0.0178	0.0178	0.0178	0.0178	0.0178	0.0178	0.0178	0.0178
immunomodulating	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059
inhibitors	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059
opioid antagonists	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237
osteoanabolic	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059
regulating	0	0	0	0	0	0	0.0059	0

renin (EC 3.4.23.1) inhibitors	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237
stimulating	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237	0.0237
All activities	1.9645	2.0059	1.9704	2.006	1.9645	2.0001	1.9822	1.9645
Percentage of activities with false- positive results [%]	17.39		13.04		13.64		13.04	

Table S6. Frequency of predicted release of bioactive fragments A_E and A_{E0} in individual genetic variants of α_{s1} -casein. Differences between sequences with and without post-translational modifications were indicated in red.

α_{s1} -CN	Variant A		Variant B		Variant C		Variant D	
Activity	A _E	A _{E0}	A _E	A _{E0}	A _E	A _{E0}	A _E	A _{E0}
ACE (EC 3.4.15.1) inhibitors	0.0376	0.043	0.0352	0.0402	0.04	0.0452	0.0352	0.0402
α -glucosidase (EC 3.2.1.20) inhibitors	0.0161	0.0161	0.0151	0.0151	0.0151	0.0151	0.0151	0.0151
anti-amnesic (proline oligopeptidase - EC 3.4.21.26 inhibitors)	0.0054	0.0054	0.005	0.005	0.005	0.005	0.005	0.005
DPPIII (EC 3.4.14.4) inhibitors	0.0269	0.0269	0.0251	0.0251	0.0251	0.0251	0.0251	0.0251
DPPIV (EC 3.4.14.5) inhibitors	0.0699	0.0699	0.0754	0.0754	0.0754	0.0754	0.0754	0.0754
stimulating	0.0161	0.0215	0.0201	0.0251	0.0151	0.0201	0.0201	0.0251
All activities	0.172	0.1828	0.1759	0.1859	0.1757	0.1859	0.1759	0.1859
Percentage of activities with false-positive results [%]	33.33		33.33		33.33		33.33	

Table S7. Frequency of predicted release of bioactive fragments A_E and A_{E0} in individual genetic variants of α_{s2} -casein. Differences between sequences with and without post-translational modifications were indicated in red.

α_{s2} -CN	Variant A		Variant B		Variant C		Variant D	
Activity	A _E	A _{E0}	A _E	A _{E0}	A _E	A _{E0}	A _E	A _{E0}
ACE (EC 3.4.15.1) inhibitors	0.0628	0.0676	0.0676	0.0725	0.058	0.0628	0.0606	0.0657
antioxidative	0.0145	0.0145	0.0145	0.0145	0.0145	0.0145	0.0152	0.0152
DPPIII (EC 3.4.14.4) inhibitors	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0051	0.0051
DPPIV (EC 3.4.14.5) inhibitors	0.1014	0.1014	0.1063	0.1063	0.1014	0.1014	0.1061	0.1061
stimulating	0.0097	0.0097	0.0097	0.0097	0.0048	0.0048	0.0101	0.0101
Total	0.1932	0.198	0.2029	0.2078	0.1835	0.1883	0.1971	0.2022
Percentage of activities with false-positive results [%]	20.00		20.00		20.00		20.00	

Table S8. Frequency of predicted release of bioactive fragments A_E and A_{E0} in individual genetic variants of β -casein. Differences between sequences with and without post-translational modifications were indicated in red.

β -CN	Variant A1		Variant A2		Variant A3		Variant B	
Activity	A _E	A _{E0}	A _E	A _{E0}	A _E	A _{E0}	A _E	A _{E0}
ACE (EC 3.4.15.1) inhibitors	0.067	0.067	0.0766	0.0766	0.0766	0.0766	0.0766	0.0766
α -glucosidase (EC 3.2.1.20) inhibitors	0	0	0	0.0191	0	0.0191	0	0.0191
anti-amnesic (proline oligopeptidase - EC 3.4.21.26 inhibitors)	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
antioxidative	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
antithrombotic	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048	0.0048
DPPIII (EC 3.4.14.4) inhibitors	0.0431	0.0431	0.0383	0.0383	0.0383	0.0383	0.0431	0.0431
DPPIV (EC 3.4.14.5) inhibitors	0.1627	0.1675	0.1627	0.1675	0.1627	0.1675	0.1675	0.1722
regulating	0.0239	0.0287	0.0239	0.0287	0.0239	0.0287	0.0239	0.0287
stimulating	0.0144	0.0191	0.0144	0.0191	0.0144	0.0191	0.0144	0.0191
All activities	0.3255	0.3398	0.3303	0.3637	0.3303	0.3637	0.3399	0.3732
Percentage of activities with false-positive results [%]	37.50		44.44		44.44		44.44	

Table S9. Frequency of predicted release of bioactive fragments A_E and A_{E0} in individual genetic variants of κ -casein. Differences between sequences with and without post-translational modifications were indicated in red.

κ -CN	Variant A		Variant B		Variant B2		Variant C	
Activity	A	A ₀	A	A ₀	A	A ₀	A	A ₀
ACE (EC 3.4.15.1) inhibitors	0.1065	0.1124	0.1124	0.1183	0.1065	0.1124	0.1065	0.1124
α -glucosidase (EC 3.2.1.20) inhibitors	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059
anti-inflammatory	0.0118	0.0118	0.0118	0.0118	0.0118	0.0118	0.0118	0.0118
antioxidative	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059
CaMPDE (EC 3.1.4.17) inhibitors	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059
DPPIV (EC 3.4.14.5) inhibitors	0.1538	0.1538	0.1538	0.1538	0.1598	0.1598	0.1538	0.1538
renin (EC 3.4.23.1) inhibitors	0.0118	0.0118	0.0118	0.0118	0.0118	0.0118	0.0118	0.0118
stimulating	0.0178	0.0178	0.0178	0.0178	0.0178	0.0178	0.0118	0.0178
All activities	0.3194	0.3253	0.3253	0.3312	0.3254	0.3313	0.3134	0.3253
Percentage of activities with false-positive results [%]	12.50		12.50		12.50		12.50	

Table S10. Percentage of false-positive (FP) results for the frequency of occurrence of bioactive fragments in sequences of individual proteins (parameter A). Annotation " $A_0 = 0$ " means no possibility of computing FP value based on Equation 3 (dividing by 0). Activities with FP = 0 for all analyzed proteins were omitted.

Protein	ACE (EC 3.4.15.1) inhibitors	antibacterial	antioxidative	DPPIV (EC 3.4.14.5) inhibitors	binding	regulating	stimulating	immunomodulating	All activities
α_{51} -CN A	2.52	0	0	3.51	0	0	24.96	0	2.91
α_{51} -CN B	2.31	0	0	3.23	0	0	21.45	0	2.61
α_{51} -CN C	2.29	0	0	3.25	0	0	22.97	0	2.63
α_{51} -CN D	2.37	0	0	4.79	0	0	21.45	0	3.12
α_{52} -CN A	2.83	0	3.27	4.73	0	0	22.3	100	4.41
α_{52} -CN B	2.81	0	3.27	4.06	0	0	17.66	$A_0 = 0$	3.6
α_{52} -CN C	2.84	0	3.27	4.7	0	0	22.3	100	4.41
α_{52} -CN D	1.94	0	3.26	4.82	0	0	13.32	100	3.67
β -CN A1	0	0	0	1.74	20.08	9.13	15.73	24.61	1.91
β -CN A2	0	0	0	1.66	16.72	9.13	14.33	20.08	1.74
β -CN A3	0	0	0	1.68	20.08	9.13	15.73	20.08	1.76
β -CN B	0	0	0	1.7	16.72	9.13	15.73	24.61	1.79
κ -CN A	0.99	8.31	9.11	1.52	0	$A_0 = 0$	0	0	2.06
κ -CN B	0.99	0	9.11	1.52	0	$A_0 = 0$	0	0	1.77
κ -CN B2	0.99	0	19.82	1.52	$A_0 = 0$	$A_0 = 0$	0	0	1.78
κ -CN C	0.99	0	8.85	1.52	$A_0 = 0$	0	0	0	1.76

Table S11. Percentage of false-positive (FP) results for the frequency of release of bioactive fragments during digestion of individual proteins (parameter A_E). Annotation " $A_{E0} = 0$ " means no possibility of computing FP values based on Equation 4 (dividing by 0). Activities with FP = 0 for all analyzed proteins were omitted.

Protein	ACE (EC 3.4.15.1) inhibitors	α -glucosidase (EC 3.2.1.20) inhibitors	DPPIV (EC 3.4.14.5) inhibitors	regulating	stimulating	All activities
α_{s1} -CN A	12.56	0	0	0	25.12	5.91
α_{s1} -CN B	12.44	0	0	0	19.92	5.38
α_{s1} -CN C	11.5	0	0	0	24.88	5.49
α_{s1} -CN D	12.44	0	0	0	19.92	5.38
α_{s2} -CN A	7.1	0	0	0	0	2.42
α_{s2} -CN B	6.76	0	0	0	0	2.36
α_{s2} -CN C	7.64	0	0	0	0	2.55
α_{s2} -CN D	7.76	0	0	0	0	2.52
β -CN A1	0	$A_{E0} = 0$	2.87	16.72	24.61	4.21
β -CN A2	0	100	2.87	16.72	24.61	9.18
β -CN A3	0	100	2.87	16.72	24.61	9.18
β -CN B	0	100	2.73	16.72	24.61	8.92
κ -CN A	5.25	0	0	$A_{E0} = 0$	0	1.81
κ -CN B	4.99	0	0	$A_{E0} = 0$	0	1.78
κ -CN B2	5.25	0	0	$A_{E0} = 0$	0	1.78
κ -CN C	5.25	0	0	$A_{E0} = 0$	33.71	3.66