

Supplementary Table 1 – Common peptide sequences between raw and heated at 63°C for 30 min ruminants' milk (bovine, ovine and caprine).

	Peptide sequence	Mass (Da)	<i>m/z</i>	Start ¹	End ²	Protein name
Bovine milk (3 peptides)	TVDMESTEVEFTKK	1514	757.87	153	165	αS2-casein
	TVDMESTEVEFTK	1386	693.83	153	164	αS2-casein
	AINPSKENLCSTFCK	1652	551.60	42	56	αS2-casein
	TGPIPNSLPQNILPLTQTPVVVPPFLQPEIMGVPK	3731	1244.70	78	112	β-casein
	YPFTGPIPN	986	987.49	75	83	β-casein
	SLSQPKVLPVPQKAVPQRDMPIQAFL	3000	750.94	179	205	β-casein
	HKEMPFKYPVEPFTESQSLTLTDVEK	3177	636.32	121	147	β-casein
	EMPFKYPVEPFTESQSL	2125	709.34	123	140	β-casein
	TPVVVPPFLQPEIMGVPK	1985	662.69	95	112	β-casein
	MPFKYPVEPFTESQS	1883	942.44	124	139	β-casein
	EPVLGPVRGPFIL	1533	767.44	208	221	β-casein
	HKEMPFKYPVEPFTESQSL	2390	598.55	121	140	β-casein
	YQEPVLGPVRGPFILV	1894	948.04	206	222	β-casein
	FQSEEQQTEDELQDKIHPFAQA	2825	942.75	48	70	β-casein
	PQNILPLTQTPVVVPPFLQPEIMGVPK	2952	984.89	86	112	β-casein
	PLTQTPVVVPPFLQPEIMGVPKVKE	2854	952.20	91	115	β-casein
	SLSQPKVLPVPQKAVPQRDMPIQA	2626	657.62	179	202	β-casein
	QEPVLGPVRGPFILV	1755	439.74	207	222	β-casein
	QQTEDELQDK	1275	638.29	54	63	β-casein
	TQTPVVVPPFLQPEIMGVPK	2214	554.55	93	112	β-casein
	SQPKVLPVPQKAVPQRDMPIQAFL	2816	704.90	181	205	β-casein
	IEKFQSEEQQTEDELQDKIHPFAQA	3115	779.88	45	70	β-casein
	QSEEQQTEDELQDK	1914	957.88	49	63	β-casein
	TPVVVPPFLQPEIM	1582	791.93	95	108	β-casein
	FQSEEQQTEDELQDKIHPFAQAQS	3040	1014.44	48	72	β-casein
	YQEPVLGPVRGPFIL	1819	607.32	206	221	β-casein
	VPPFLQPEIMGVPKVKE	1907	636.70	99	115	β-casein
	QPPQLPPTVMFPPQ	1656	828.93	161	175	β-casein
	QPPQLPP	872	873.48	161	168	β-casein
	EPVLGPVRGPF	1307	654.36	208	219	β-casein

Ovine milk (95 peptides)	KFQSEEQQTEDELQDK	2109	703.99	47	63	β -casein
	QPKVLPVPQ	1005	503.31	182	190	β -casein
	YQEPVL	747	748.39	206	211	β -casein
	EPVLPVVR	866	433.76	208	215	β -casein
	LPVPQKAVPQRDMPIQ	1816	606.34	186	201	β -casein
	QNILPLTQTPVVVPPFL	1858	930.04	87	103	β -casein
	FTGPIPNLSPQNILPLTQTPVVVPPFLQPEIMGVPK	3878	970.54	77	112	β -casein
	EQEELNVVGETVESLSSEESITHIN	3018	1510.13	17	42	β -casein
	TDVEKLHLPLPLVQS	1686	562.98	143	157	β -casein
	DMPIQA	689	690.31	197	202	β -casein
	MPFPKYPVEPFTES	1668	834.90	124	137	β -casein
	PLTQTPVVVPPFLQPEIMGVPKVKET	2845	949.20	91	116	β -casein
	VPQRDMPIQAFL	1430	715.88	193	204	β -casein
	VPPFLQPEIMGVPKVKETMVPK	2479	620.85	99	120	β -casein
	EQEELNVV	940	471.23	17	24	β -casein
	QSEEQQTEDELQDKIHQAQAQS	2813	938.77	49	72	β -casein
	EELNVVGETVESLSSEESITHIN	2681	1341.60	19	42	β -casein
	EELNVVGETVESLSSEESITHINK	2809	937.44	19	43	β -casein
	VQSWMHQPPQPLPTVMFPPQSV	2643	882.11	155	177	β -casein
	TQTPVVVPPFLQPEIMGVPKVKE	2548	850.47	93	115	β -casein
	LNENKVL	870	1462.68	105	111	β -lactoglobulin
	GTQYTDAPSFSDIPNPIGSENSGKITMP	2923	1387.66	185	212	α S1-casein
	TDAPSFSDIPNPIGSENSGKITMPLW	2773	644.35	189	214	α S1-casein
	NVPQLEIVPKSAEEQLH	1930	609.31	120	136	α S1-casein
	NPIGSENSGKIT	1217	1131.55	199	210	α S1-casein
	YLPLGTQYTDAPSFSDIPNPIGSENSGKITMP	3392	1078.53	181	212	α S1-casein
	SDIPNPIGSENSGKITMPLW	2155	698.70	195	214	α S1-casein
	YNVPQLEIVPKSAEEQLH	2093	576.29	119	136	α S1-casein
	KYNVPQLEIVPKSAEEQLH	2301	903.92	118	136	α S1-casein
	AGSSSSSEIVPNSAEQK	1806	710.71	77	94	α S1-casein
KHQGLSPEVLNENLLRF	2129	748.66	22	38	α S1-casein	
SKDIGSESIQAMEDAKQM	2243	630.81	56	75	α S1-casein	
KYNVPQLEIVPKSAEEQLHSM	2519	723.35	118	138	α S1-casein	

NPIGSENSGKITMP	1445	1065.42	199	212	α S1-casein
AGSSSSSEEIVPNSAEQKY	2129	1195.55	77	95	α S1-casein
DAPSFSDIPNPIGSENSGKITMP	2389	949.93	190	212	α S1-casein
GSSSSSEEIVPNSAEQKY	1898	771.39	78	95	α S1-casein
YNVPQLEIVPKSAEEQLHSM	2311	411.92	119	138	α S1-casein
VLNENLLRFV	1233	493.48	30	39	α S1-casein
LKKYNVPQLEIVPKSAEEQLH	2462	633.85	116	136	α S1-casein
KPWTQPKTNAI	1266	697.80	207	217	α S2-casein
DMESTEVFTKK	1394	641.75	156	166	α S2-casein
DMESTEVFTK	1281	643.11	156	165	α S2-casein
VNREQLSTSEENSKKTIDMESTEVFTK	3210	1154.39	139	165	α S2-casein
DMESTEVFT	1153	943.41	156	164	α S2-casein
SIRSSSEESA EVAPEEV	1885	987.40	69	85	α S2-casein
CTTSCEEVVRNANEEY	1973	655.28	52	68	α S2-casein
CTTSCEEVVRNA	1309	562.74	52	63	α S2-casein
CTTSCEEVVR	1123	703.68	52	61	α S2-casein
SSSEEPINISQEIYKQEK	2108	639.30	23	40	α S2-casein
EHVSSSEEPINISQEIYKQEK	2553	676.06	20	40	α S2-casein
MEHVSSEEPINISQEIYKQEK	2700	574.89	19	40	α S2-casein
HKMEHVSSEEPINISQEIYKQEK	2869	648.49	17	40	α S2-casein
KHKMEHVSSEEPINISQEIYKQEK	3237	809.70	16	40	α S2-casein
EHVSSSEEPINISQEIYKQE	2426	686.33	20	39	α S2-casein
HKMEHVSSEEPINISQEIYKQE	2741	723.67	17	39	α S2-casein
EHVSSSEEPINISQEIYK	2168	1639.21	20	37	α S2-casein
VVNAVDNPEASSESIASAPETNTAQVTSTEV	3276	1403.15	162	192	κ -casein
AVDNPEASSESIASAPETNTAQVTSTEV	2804	1447.60	165	192	κ -casein
VDNPEASSESIASAPETNTAQVTSTEV	2893	1540.14	166	192	κ -casein
NAVDNPEASSESIASAPETNTAQVTSTEV	3078	1243.54	164	192	κ -casein
PEASSESIASAPETNTAQVTSTEV	2485	407.46	169	192	κ -casein
DSVSSEVN	915	572.28	271	278	Osteopontin
DPNHFRPAGLPNKY	1626	526.05	134	147	Serum amyloid A protein
GPGGVW	571	436.25	65	70	Serum amyloid A protein
GMTRDQVREDTKADQFANEWGR	2625	916.33	92	113	Serum amyloid A protein

	RPAGLPNKY	1016	508.78	139	147	Serum amyloid A protein
	GNYDAAQRGPGGVW	1445	723.33	57	70	Serum amyloid A protein
	INHQGLSPEVPNENLL	1773	591.98	20	35	α 1-casein
	KYNVPQLEIVPKSAEEQLHSM	2519	630.81	117	137	α 1-casein
	QGLSPEVLNENLLR	1581	791.44	24	37	α 1-casein
	IDMESTEVFTK	1379	690.30	155	165	α S2-casein
	KTIDMESTEVFTK	1608	536.92	153	165	α S2-casein
	RNAGPFTPTVNREQLSTSEENS	2513	838.71	130	151	α S2-casein
	TIDMESTEVFTK	1496	748.82	154	165	α S2-casein
	QEPVLGPVR	977	977.54	207	215	β -casein
	QEPVLGPVRGPF	1375	688.37	207	219	β -casein
	QEPVLGPVRGPFPI	1488	744.92	207	220	β -casein
Caprine milk (22 peptides)	QEPVLGPVRGPFPIIL	1601	801.46	207	221	β -casein
	REQEELNVVG	1172	586.80	16	25	β -casein
	REQEELNVVGETVESLSSSEESITHIN	3094	1032.47	16	42	β -casein
	REQEELNVVGETVESLSSSEESITHINK	3302	826.62	16	43	β -casein
	REQEELNVVGETVESLSSSEESITHINKKIE	3593	719.55	16	46	β -casein
	YQEPVLGPVRGPFPIILV	1918	480.51	206	222	β -casein
	QNQNPKLPLSILKEKQL	1990	498.55	78	94	Glycosylation-dependent cell adhesion molecule 1
	ETNTAQVTSTEV	1359	680.29	181	192	κ -casein
	IVNTVDNPEASSES	1541	771.32	162	175	κ -casein
	DQFANEWGR	1121	561.75	106	114	Serum amyloid A protein
	KDPNHFGPADLPDKY	1713	571.95	114	128	Serum amyloid A protein
	RGPGGAWAAKVISNA	1454	485.60	65	79	Serum amyloid A protein

¹**Start:** Starting position of peptide in the complete protein sequence.

²**End:** Ending position peptide in the complete protein sequence.

Supplementary Table 2 – Common peptide sequences between raw and heated at 85°C for 5 min ruminants' milk (bovine, ovine and caprine).

	Peptide sequence	Mass (Da)	<i>m/z</i>	Start ¹	End ²	Protein name
Bovine milk (5 peptides)	QEPVLGPVR	977	977.54	209	217	β-casein
	TVDMESTEVEFTK	1402	701.82	153	164	αS2-casein
	PEVIESPPEINTVQVTSTAV	2109	1055.55	171	190	κ-casein
	QPQSQNPKLPLSIL	1545	773.44	75	88	Glycosylation-dependent cell adhesion molecule 1
	SSRQPQSQNPKLPLSILKEK	2259	452.86	72	91	Glycosylation-dependent cell adhesion molecule 1
Ovine milk (41 peptides)	QNILPLTQTPVVVPPFLQPEIMGVPK	2838	1419.79	87	112	β-casein
	QPKVLPVPQK	1116	558.84	182	191	β-casein
	QPPQPLPPTVMFPPQSV	1842	921.98	161	177	β-casein
	EQEELNVVGETVESLSSEESITHIN	2858	1430.17	17	42	β-casein
	TQTPVVVPPFLQPEIMGVPK	2192	731.74	93	112	β-casein
	IEKFQSEEQQTEDELQDK	2351	784.70	45	63	β-casein
	LTQTPVVVPPFLQPEIMGVPK	2305	769.43	92	112	β-casein
	KIEKFQSEEQQTEDELQDKIHPF	2973	595.70	44	67	β-casein
	TGPIPNLQPNILPLTQTPVVVPPFLQPEIMGVPK	3747	1250.03	78	112	β-casein
	MPPFKYPVEP	1204	602.81	124	133	β-casein
	PLTQTPVVVPPFLQPEIMGVPKV	2515	1258.71	91	113	β-casein
	PLTQTPVVVPPFLQPEI	1874	938.03	91	107	β-casein
	QPPQPLPPTVMFPPQS	1776	888.95	161	176	β-casein
	QSEEQQTEDELQDK	1818	909.90	49	63	β-casein
	QNILPLTQTPVVVPPFLQPEIMGVPKVKETMVPK	3799	950.78	87	120	β-casein
	SWMHQPPQPLPPTVMFPPQSV	2400	801.07	157	177	β-casein
	PQNILPLTQTPVVVPPFLQPEI	2440	1221.20	86	107	β-casein
	NPIGSENSGKITMP	1444	722.86	199	212	αS1-casein
	YLPLGTQYTDAPSFSDIPNPIGSENSGKITMP	3426	1142.88	181	212	αS1-casein
	TDAPSFSDIPNPIGSENSGKITMP	2474	1238.08	189	212	αS1-casein
	LPLGTQYTDAPSFSDIPNPIGSENSGKITMP	3263	1088.53	182	212	αS1-casein
	IPNPIGSENSGKITMP	1654	827.93	197	212	αS1-casein
	GSSSSSEEIVPNSAEQKY	1978	989.92	78	95	αS1-casein
AGSSSSSEEIVPNSAEQK	1886	943.91	77	94	αS1-casein	
VNREQLSTSEENSKKTIDMESTEVEFTK	3210	643.11	139	165	αS2-casein	

	DMESTEVFT	1073	1074.43	156	164	α S2-casein
	SIRSSSEESA EVAPEEV	1805	903.42	69	85	α S2-casein
	CTTSCEEVVR	1123	562.74	52	61	α S2-casein
	MEHVSSSEEPINISQEIYKQEK	2684	672.06	19	40	α S2-casein
	HKMEHVSSSEEPINISQEIYKQEK	2885	578.09	17	40	α S2-casein
	KHKMEHVSSSEEPINISQEIYKQEK	3157	632.49	16	40	α S2-casein
	EHVSSSEEPINISQEIYK	2168	723.67	20	37	α S2-casein
	EHVSSSEEPINISQE	1764	882.87	20	34	α S2-casein
	EHVSSSEEPINI	1340	670.82	20	31	α S2-casein
	VVNAV DNPEASSESIASAPETNTAQVTSTEV	3196	1599.22	162	192	κ -casein
	PEASSESIASAPETNTAQVTSTEV	2565	1283.53	169	192	κ -casein
	NTAQVTSTEV	1128	1129.47	183	192	κ -casein
	AVDNPEASSESIASAPETNTAQVTSTEV	2884	1443.13	165	192	κ -casein
	VDNPEASSESIASAPETNTAQVTSTEV	2893	1447.58	166	192	κ -casein
	SNVESPDATEEDF	1519	1519.55	170	182	Osteopontin
	NVESPDATEEDF	1352	1352.55	171	182	Osteopontin
	YNVPQLEIVPK	1313	1313.72	118	128	α S1-casein
	KTIDMESTEVFTK	1624	812.86	153	165	α S2-casein
	KIEKFQSEEQQQTEDELQDK	2559	1280.56	44	63	β -casein
	KKIEKFQSEEQQQTEDELQD	2560	1281.07	43	62	β -casein
Caprine milk (10 peptides)	QEELNVVG	886	887.45	18	25	β -casein
	REQEELNVVGETVESLSSSEESITHINK	3222	1075.17	16	43	β -casein
	QDENYEEAIVHLK	1570	785.87	128	140	Butyrophilin subfamily 1 member A1
	QNQNPKLPLSILKE	1621	541.31	78	91	Glycosylation-dependent cell adhesion molecule 1
	KDSKADQFANEWG	1533	767.32	101	113	Serum amyloid A protein
	REAGQGAKDMW	1264	632.79	26	36	Serum amyloid A protein

¹**Start:** Starting position of peptide in the complete protein sequence.

²**End:** Ending position peptide in the complete protein sequence.

Supplementary Table 3 - Peptides found in each treatment (raw, 63°C/30 min and 85°C/5 min) and species (bovine, ovine and caprine) combination that have an exact match with the bioactive peptides database (MBPDB)

	Treatment	Peptide	Protein description	Function	Reference
Bovine milk	Raw (3 peptides)	LPQNIPPLT	β -casein	DPP-IV inhibitory	Nongonierma and FitzGerald (2016)
		LPLP	β -casein	ACE-inhibitory	Kohmura et al. (1990)
		TPEVDDEALEK	β -lactoglobulin	DPP-IV inhibitory	Silveira et al. (2013)
	63°C/30 min (5 peptides)	FPEVFGK	α S1-casein	ACE-inhibitory	Maruyama et al. (1987)
		RELEELNVPGEIVESLSSEESITR	β -casein	Immunomodulatory	Hata et al. (1998)
		VLPVPQKAVPYPQR	β -casein	Antimicrobial	Sedaghati et al. (2016)
		EPVLPVVRGPF	β -casein	ACE-inhibitory	Hayes et al. (2007)
		LIVTQTMK	β -lactoglobulin	Cytotoxic	Jacquot (2010)
	85°C/5 min (3 peptides)	QMEAESISSSEEIVPNSVEQK	α S1-casein	Immunomodulatory	Hata et al. (1998)
		NMAINPSKENLCSTFCK	α S2-casein	ACE-inhibitory	Tu et al. (2018)
		RELEELNVPGEIVESLSSEESITR	β -casein	Immunomodulatory	Hata et al. (1998)
	Raw (26 peptides)	DAYPSGAW	α S1-casein	ACE-inhibitory	Pihlanto-Leppälä et al. (1998)
		RYL	α S1-casein	Antioxidant	Contreras et al. (2013)
		VLNENLLR	α S1-casein	Antimicrobial	Hayes et al. (2006)
		YLEQLLR	α S1-casein	Antimicrobial	Liu et al. (2015)
YLGYLEQ		α S1-casein	Anxiolytic	Cakir-Kiefer et al. (2011)	
VPSELYL		α S1-casein	ACE-inhibitory	Ruiz et al. (2004)	
NPWDQ		α S2-casein	Immunomodulatory	Isobe et al. (2008)	
VRYL		α S2-casein	ACE-inhibitory	Ruiz et al. (2004)	
YQKFPQY		α S2-casein	ACE-inhibitory	Silva et al. (2006)	
HLPLP		β -casein	ACE-inhibitory	Kohmura et al. (1990)	
LPLP		β -casein	ACE-inhibitory	Kohmura et al. (1990)	
EPVLPVVRGPF		β -casein	ACE-inhibitory	Hayes et al. (2007)	
GPFPI		β -casein	Cathepsin B Inhibitory	Lee and Lee (2000)	
LPVP		β -casein	DPP-IV inhibitory	Nongonierma et al. (2018)	
LPVPQ		β -casein	DPP-IV inhibitory	Nongonierma and FitzGerald (2016)	
MPFPKYPVEP	β -casein	ACE-inhibitory	Hayes et al. (2007)		
YQEPVLGP	β -casein	Antioxidant	Silva et al. (2006)		

Ovine milk		YQEPVLGPVRGPFPI	β -casein	Antimicrobial	Almaas et al. (2011)	
		TPVVVPPFLQP	β -casein	ACE-inhibitory	Abubakar et al. (1998)	
		VLPVPQK	β -casein	Antioxidant	Shanmugam et al. (2015)	
		YPVEPFTE	β -casein	Bradykinin-Potentiating	Perpetuo et al. (2003)	
		YQEPVL	β -casein	ACE-inhibitory	Pihlanto-Leppälä et al. (1998)	
		HPHPHLSF	κ -casein	ACE-inhibitory	Gómez-Ruiz et al. (2007)	
		IPIQY	κ -casein	ACE-inhibitory	Nongonierma and FitzGerald (2014)	
		YIPIQY	κ -casein	DPP-IV inhibitory	Gómez-Ruiz et al. (2007)	
		LRP	Lactotransferrin	ACE-inhibitory	García-Tejedor et al. (2014)	
	63°C/30 min (15 peptides)		FPQYLQY	α S2-casein	ACE-inhibitory	Tauzin et al. (2002)
			FPQY	α S2-casein	ACE-inhibitory	Contreras et al. (2013)
			EPVLGPVRGPF	β -casein	ACE-inhibitory	Hayes et al. (2007)
			YQEPVL	β -casein	ACE-inhibitory	Pihlanto-Leppälä et al. (1998)
			QSLVYP	β -casein	ACE-inhibitory	Kohmura et al. (1990)
			EPVLGPVRGP	β -casein	Cytomodulatory	Zhao et al. (2014)
		LPQNILP	β -casein	ACE-inhibitory	Kohmura et al. (1990)	
		LPLPL	β -casein	DPP-IV inhibitory	Nongonierma and FitzGerald (2014)	
		YPVEPF	β -casein	DPP-IV inhibitory	Nongonierma and FitzGerald (2016)	
		QEPVL	β -casein	immunomodulatory	Jiehui et al. (2014)	
		YQEPVLGPVR	β -casein	Immunomodulatory	Kayser and Meisel (1996)	
		YPVEPF	β -casein	Opioid	Plaisancié et al. (2015)	
		IYP	β -casein	ACE-inhibitory	Kohmura et al. (1990)	
		IIVTQTMK	β -lactoglobulin	Antimicrobial	Almaas et al. (2011)	
		YPSYGLN	κ -casein	Opioid	Meisel et al. (1989)	
85°C/5 min (7 peptides)		GPFPILV	β -casein	DPP-IV inhibitory	Zhang et al. (2016)	
		LVYP	β -casein	ACE-inhibitory	Kohmura et al. (1990)	
		LVYPFTGPIP	β -casein	ACE-inhibitory	Quirós et al. (2005)	
		MPFPKYPVEP	β -casein	ACE-inhibitory	Hayes et al. (2007)	
		QSLVYP	β -casein	ACE-inhibitory	Kohmura et al. (1990)	
		REQEELNV	β -casein	Antimicrobial	Kohmura et al. (1990)	
		TQTPVVVPPFLQPE	β -casein	Antioxidant	Sabeena Farvin et al. (2010)	
Raw	DAYPSGAW	α S1-casein	ACE-inhibitory	Pihlanto-Leppälä et al. (1998)		

Caprine milk	(12 peptides)	VLNENLLR	α S1-casein	Antimicrobial	Hayes et al. (2006)
		EPVLGPVRGPF	β -casein	ACE-inhibitory	Hayes et al. (2007)
		GPFILV	β -casein	DPP-IV inhibitory	Zhang et al. (2016)
		KIHPFAQAQ	β -casein	ACE-inhibitory	Quirós et al. (2005)
		REQEELNV	β -casein	Antimicrobial	Almaas et al. (2011)
		YQEPVL	β -casein	ACE-inhibitory	Pihlanto-Leppälä et al. (1998)
		YQEPVLGP	β -casein	Antioxidant	Silva et al. (2006)
		YQEPVLGPVR	β -casein	Immunomodulatory	Lu et al. (2016)
		YQEPVLGPVRGPFPI	β -casein	Antimicrobial	Almaas et al. (2011)
		YIPIQY	κ -casein	ACE-inhibitory	Gómez-Ruiz et al. (2007)
		YVL	κ -casein	Antioxidant	López-Expósito et al. (2007)
		QEPVL	β -casein	Immunomodulatory	Jiehui et al. (2014)
	63°C/30 min (4 peptides)	LVYP	β -casein	ACE-inhibitory	Kohmura et al. (1990)
	VLPVPQK	β -casein	Antioxidant	Shanmugam et al. (2015)	
	TQTPVVVPPFLQPE	β -casein	Antioxidant	Sabeena Farvin et al. (2010)	
85°C/5 min (1 peptide)	LVYPFTGPIP	β -casein	ACE-inhibitory	Quirós et al. (2005)	

References

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