

Figure S1. Venn diagram analysis of the identified peptides from α_1 -casein (A), α_2 -casein (B), β -casein (C), κ -casein (D) and β -Lg (E) in raw milk (RM), pasteurized milk (PM0d), pasteurized milk upon 3 days storage (PM3d) and pasteurized milk upon 7 days storage (PM7d) under the whole in vitro digestion.

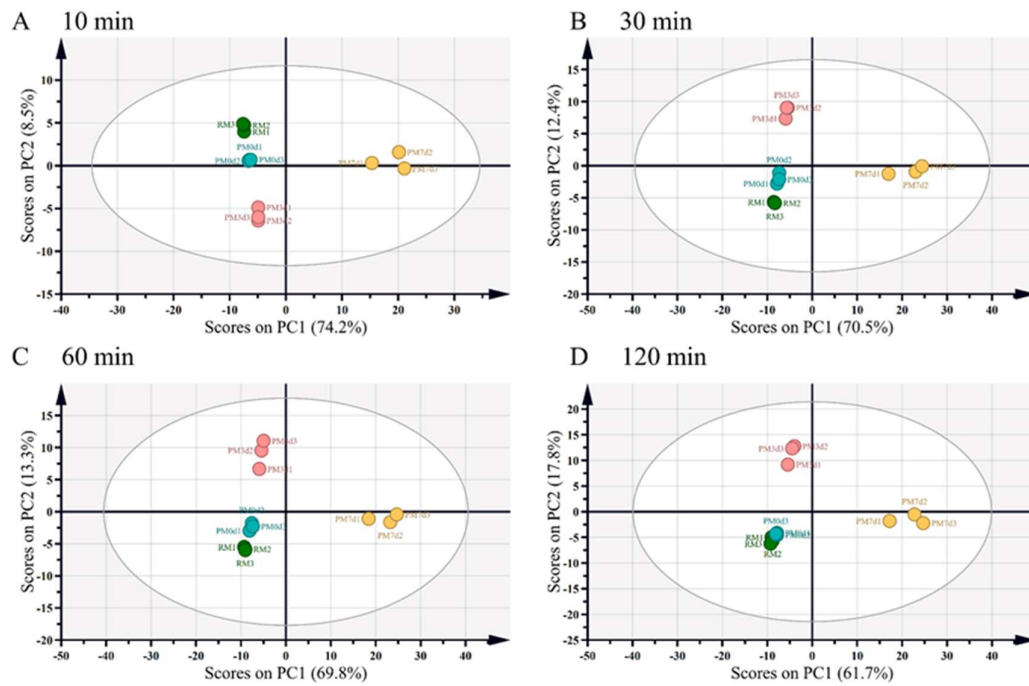


Figure S2. PCA score plots of the identified peptides from raw milk (RM), pasteurized milk (PM0d), pasteurized milk upon 3 days storage (PM3d) and pasteurized milk upon 7 days storage (PM7d) at 10, 30, 60 and 120 min of the in vitro gastric digestion.

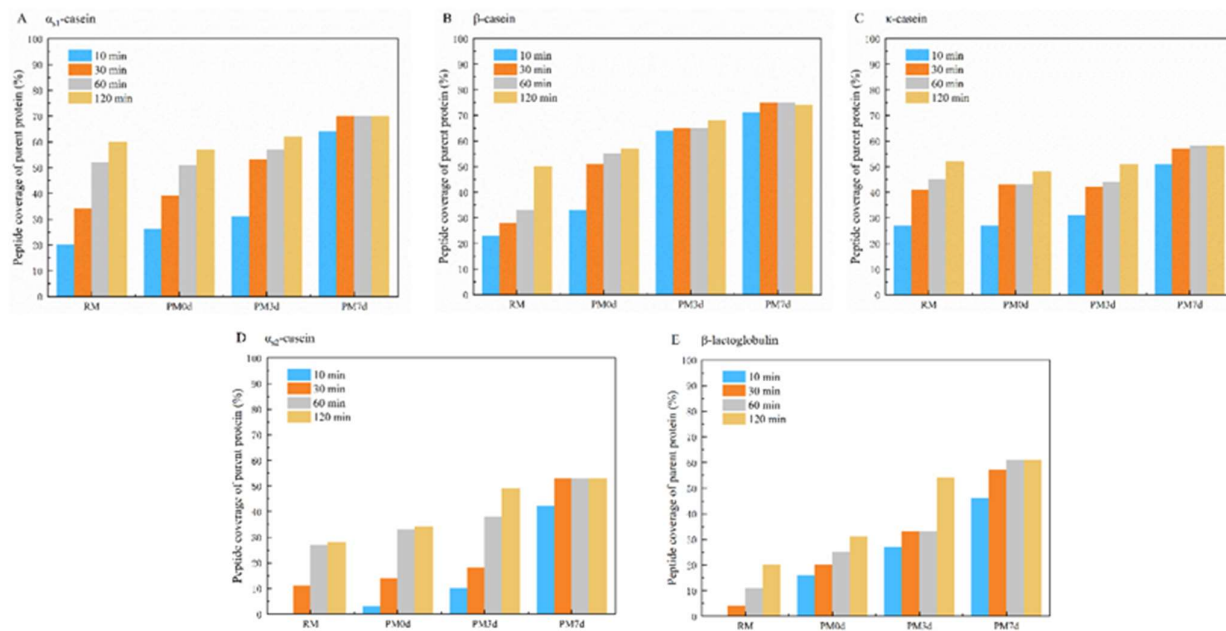


Figure S3. Peptide coverages of parent protein sequences (A: α_1 -casein, B: β -casein, C: κ -casein, D: α_2 -casein and E: β -lactoglobulin) from raw milk (RM), pasteurized milk (PM0d), pasteurized milk upon 3 days storage (PM3d) and pasteurized milk upon 7 days storage (PM7d) at 10, 30, 60 and 120 min of digestion.

B α S2-casein

peptides 1

| 9

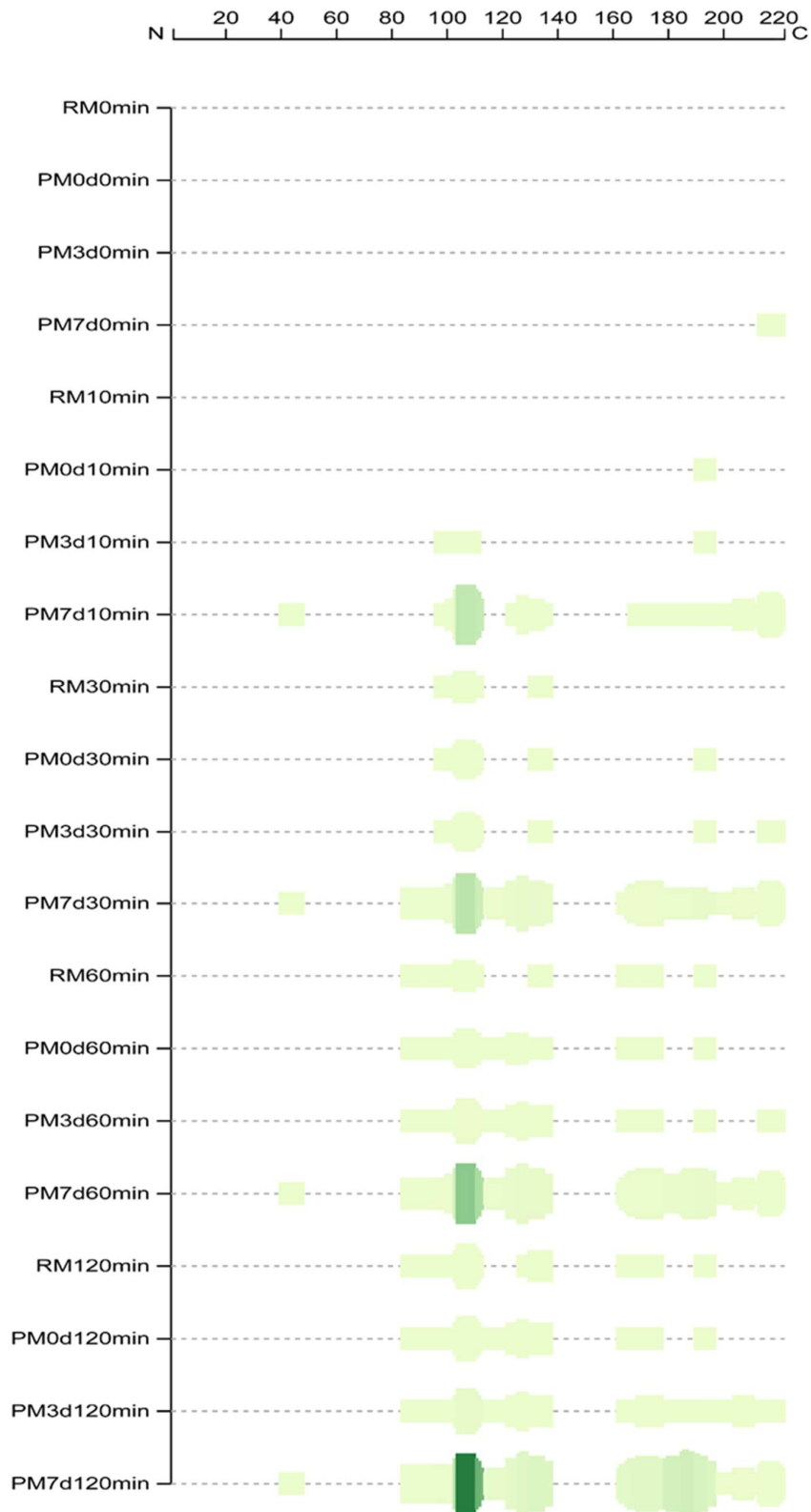
intensity 0

4.2E+9

8.4E+9

1.3E+10

1.7E+10



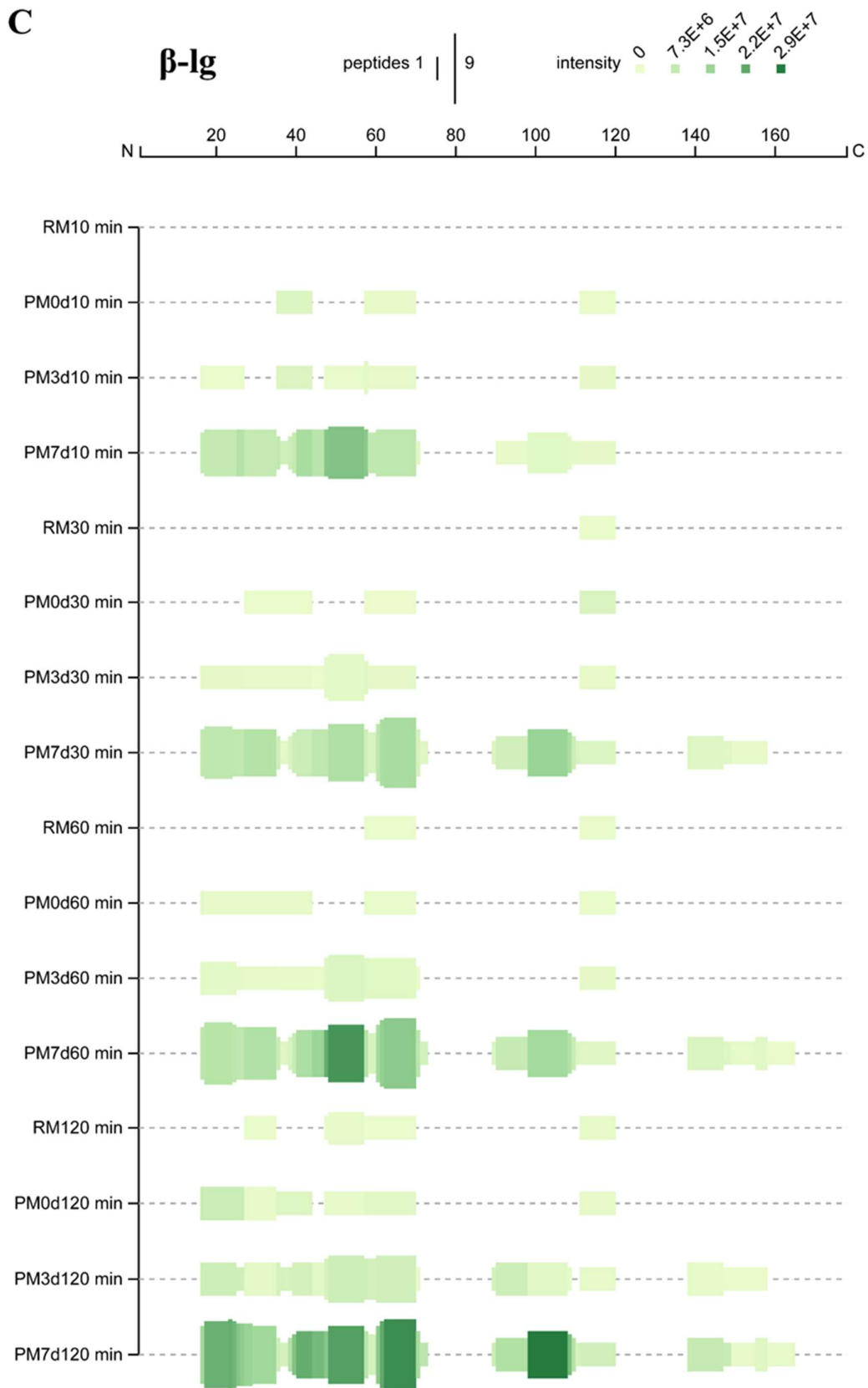


Figure S5. Peptide profiles originating from κ -casein (A), α_2 -casein (B) and β -lactoglobulin (β -lg, C) during in vitro gastric digestion of raw milk (RM), pasteurized milk (PM0d), pasteurized milk upon 3 days storage (PM3d) and pasteurized milk upon 7 days storage (PM7d).

Table 1. List of references for the bioactive peptides in Table 1.

Ref No.	Reference
1	Robert, M. C., Razaname, A., Mutter, M., & Juillerat, M. A. (2004). Identification of angiotensin-I-converting enzyme inhibitory peptides derived from sodium caseinate hydrolysates produced by <i>Lactobacillus helveticus</i> NCC 2765. <i>Journal of Agricultural and Food Chemistry</i> , 52(23), 6923-6931.
2	McCann, K. B., Shiell, B. J., Michalski, W. P., Lee, A., Wan, J., Roginski, H., & Coventry, M. J. (2006). Isolation and characterisation of a novel antibacterial peptide from bovine α S1-casein. <i>International Dairy Journal</i> , 16(4), 316-323.
3	Tang, W., Yuan, H., Zhang, H., Wang, L., Qian, H., & Qi, X. (2015). An antimicrobial peptide screened from casein hydrolyzate by <i>Saccharomyces cerevisiae</i> cell membrane affinity method. <i>Food control</i> , 50, 413-422.
4	Totsuka, M., Kakehi, M., Kohyama, M., Hachimura, S., Hisatsune, T., & Kaminogawa, S. (1998). Enhancement of antigen-specific IFN- γ production from CD8+ T cells by a single amino acid-substituted peptide derived from bovine α s1-casein. <i>Clinical immunology and immunopathology</i> , 88(3), 277-286.
5	Pihlanto-Leppälä, A., Rokka, T., & Korhonen, H. (1998). Angiotensin I converting enzyme inhibitory peptides derived from bovine milk proteins. <i>International Dairy Journal</i> , 8(4), 325-331.
6	Hayes, M., Ross, R. P., Fitzgerald, G. F., Hill, C., & Stanton, C. (2006). Casein-derived antimicrobial peptides generated by <i>Lactobacillus acidophilus</i> DPC6026. <i>Appl. Environ. Microbiol.</i> , 72(3), 2260-2264.
7	Coste, M., Rochet, V., Léonil, J., Mollé, D., Bouhallab, S., & Tomé, D. (1992). Identification of C-terminal peptides of bovine β -casein that enhance proliferation of rat lymphocytes. <i>Immunology Letters</i> , 33(1), 41-46.
8	Lu, Y., Govindasamy-Lucey, S., & Lucey, J. A. (2016). Angiotensin-I-converting enzyme-inhibitory peptides in commercial Wisconsin Cheddar cheeses of different ages. <i>Journal of dairy science</i> , 99(1), 41-52.
9	Kayser, H., & Meisel, H. (1996). Stimulation of human peripheral blood lymphocytes by bioactive peptides derived from bovine milk proteins. <i>FEBS letters</i> , 383(1-2), 18-20.
10	Sagardia, I., Iloro, I., Elortza, F., & Bald, C. (2013). Quantitative structure-activity relationship based screening of bioactive peptides identified in ripened cheese. <i>International Dairy Journal</i> , 33(2), 184-190.
11	Sandré, C., Gleizes, A., Forestier, F., Gorges-Kergot, R., Chilmonczyk, S., Léonil, J., ... & Labarre, C. (2001). A peptide derived from bovine β -casein modulates functional properties of bone marrow-derived macrophages from germfree and human flora-associated mice. <i>The Journal of nutrition</i> , 131(11), 2936-2942.
12	Rojas-Ronquillo, R., Cruz-Guerrero, A., Flores-Nájera, A., Rodríguez-Serrano, G., Gómez-Ruiz, L., Reyes-Grajeda, J. P., ... & García-Garibay, M. (2012). Antithrombotic and angiotensin-converting enzyme inhibitory properties of peptides released from bovine casein by <i>Lactobacillus casei</i> Shirota. <i>International Dairy Journal</i> , 26(2), 147-154.
13	Birkemo, G. A., O'Sullivan, O., Ross, R. P., & Hill, C. (2009). Antimicrobial activity of two peptides casecidin 15 and 17, found naturally in bovine colostrum. <i>Journal of applied microbiology</i> , 106(1), 233-240.
14	Yamamoto, N., Akino, A., & Takano, T. (1994). Antihypertensive effect of the peptides derived from casein by an extracellular proteinase from <i>Lactobacillus helveticus</i> CP790. <i>Journal of dairy science</i> , 77(4), 917-922.
15	Lopez-Exposito, I., Minervini, F., Amigo, L., & Recio, I. (2006). Identification of antibacterial peptides from bovine κ -casein. <i>Journal of food protection</i> , 69(12), 2992-2997.
16	Miguel, M., Gómez-Ruiz, J. Á., Recio, I., & Aleixandre, A. (2010). Changes in arterial blood pressure after single oral administration of milk-casein-derived peptides in spontaneously hypertensive rats. <i>Molecular nutrition & food research</i> , 54(10), 1422-1427.
17	Robitaille, G., Lapointe, C., Leclerc, D., & Britten, M. (2012). Effect of pepsin-treated bovine and goat caseinomacropptide on <i>Escherichia coli</i> and <i>Lactobacillus rhamnosus</i> in acidic conditions. <i>Journal of dairy science</i> , 95(1), 1-8.
18	Jacquot, A., Gauthier, S. F., Drouin, R., & Boutin, Y. (2010). Proliferative effects of synthetic peptides from β -lactoglobulin and α -lactalbumin on murine splenocytes. <i>International dairy journal</i> , 20(8), 514-521.
19	Lacroix, I. M., Meng, G., Cheung, I. W., & Li-Chan, E. C. (2016). Do whey protein-derived peptides have dual dipeptidyl-peptidase IV and angiotensin I-converting enzyme inhibitory activities? <i>Journal of functional foods</i> , 21, 87-96.

- 20 Tavares, T., del Mar Contreras, M., Amorim, M., Pintado, M., Recio, I., & Malcata, F. X. (2011).
Novel whey-derived peptides with inhibitory effect against angiotensin-converting enzyme: in vitro
effect and stability to gastrointestinal enzymes. *Peptides*, 32(5), 1013-1019.
- 21 Tavares, T. G., & Malcata, F. X. (2012). The Portuguese Paradox: Why do some inhabitants of
Portugal appear to live so long when their diet is based on whey cheese? *Food chemistry*, 131(3),
727-729.
- 22 Lacroix, I. M., & Li-Chan, E. C. (2014). Isolation and characterization of peptides with dipeptidyl
peptidase-IV inhibitory activity from pepsin-treated bovine whey proteins. *Peptides*, 54, 39-48.
-