New Developments and Applications of Bacteriocins and Peptides in Foods

S. Mills,[1] C. Stanton,[1,2,3] C. Hill,[1,3,4] and R.P. Ross[1,2,3]

[1]Food for Health Ireland, Moorepark Food Research Center, Fermoy, County Cork, Ireland; email: paul.ross@teagasc.ie

[2]Teagasc, Moorepark Food Research Center, Fermoy, County Cork, Ireland

[3]Alimentary Pharmabiotic Center, University College Cork, Cork, Ireland

[4]Department of Microbiology, University College Cork, Cork, Ireland

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Abstract

There is an increased desire for sophisticated foods, whereby consumers harbor higher expectations of health-promoting benefits above basic nutrition. Moreover, there is a move from the adulteration of foods with chemical preservatives toward biopreservation. Such expectations have led scientists to identify novel approaches to satisfy both demands, which utilize bacteriocin and peptide-based solutions. The best known examples of biopreservation involve bacteriocins. However, with the exception of nisin, bacteriocins have received limited use in the food industry. Peptides can be added to foods to improve consumer health. Some of the best known examples are angiotensin I–converting enzyme (ACE)-inhibitory peptides, which inhibit ACE, a key enzyme involved in blood pressure (BP) regulation. To be effective, these peptides must be bioavailable, but by their nature, peptides are degraded by digestion with proteolytic enzymes. This review critically discusses the use and potential of peptides and bacteriocins in food systems in terms of safety, quality, and improvement of human health.

INTRODUCTION

When considering new applications of bacteriocins and peptides in food systems, three criteria spring to mind, namely safety, quality, and nutrition/health, that are among the key issues driving continued efforts in food research and development. Remarkably, bacteriocins and peptides have the potential to affect all aspects of these three criteria from microbial quality and safety to taste perception and allerginicity, and even to health promotion through a range of biological activities that can be as diverse as drug-type effects on the central nervous system. Although bacteriocins and peptides are completely unrelated molecules in terms of functionalities, they are both composed of unique sequences of amino acids. Bacteriocins are ribosomally synthesized, heat-stable, antimicrobial peptides produced by one bacterium [which is immune to its own bacteriocin(s)] and are active against other bacteria, either in the same species (narrow spectrum of activity) or across genera (broad spectrum of activity) (Cotter et al. 2005). Bacteriocins generally act through depolarization of the target cell membrane or through inhibition of cell wall synthesis (Abee et al. 1995). They usually range from 30–60 amino acids in length and have been associated with numerous species of bacteria. However, the bacteriocins of lactic acid bacteria (LAB) have received much attention in terms of food safety due to their generally recognized as safe (GRAS) status (Settanni & Corsetti 2008). They can be readily introduced into fermented foods without prior purification or concentration (Cotter et al. 2005), and they exhibit activity against key Gram-positive pathogens such as *Listeria monocytogenes* and *Staphylococcus aureus* (Sobrino-López & Martín-Belloso 2008b). Although they generally don't target Gram-negative bacteria, bacteriocins may be effective at killing Gram-negatives if the outer membrane is destabilized (Stevens et al. 1991). However, despite a wealth of bacteriocins that have been investigated as potential biopreservatives for the food industry, to date only two LAB bacteriocins, namely nisin and pediocin PA-1, are commercially available. Nisin is available as a dried concentrated powder called Nisaplin (Danisco) and was admitted into the European food additive list in the early 1980s, where it was assigned the number E234 (EEC 1983). It has since received GRAS status by the Food and Drug Administration (FDA) (Federal Register 1988), and it is the only bacteriocin that has been approved by the World Health Organization for use as a food preservative (Sobrino-López & Martín-Belloso 2008b). Pediocin PA-1 is commercially exploited as a bacteriocin-containing fermentate powder, namely ALTA® 2351 (Kerry Bioscience).

Bioactive peptides have the potential to regulate a range of physiological functions of the body. They can be encrypted in the polypeptide chain of proteins and can be released via proteolysis, where they may interact with appropriate receptors, exhibiting hormone-like activity (Dziuba & Darewicz 2007). They generally contain between 3 and 20 amino acids (Pihlanto 2001), but may be larger in some cases. However, food-derived bioactive peptides generally contain two to nine amino acids (Möller et al. 2008). Their activity depends on their amino acid composition and sequence (Shahidi & Zhong 2008), and various bioactivities have been reported, including peptides that reduce blood pressure (BP) (antihypertensive peptides), antithrombotic peptides, opioid peptides, casein phospopeptides (CPP), antimicrobial peptides, cytomodulatory peptides, and immunomodulatory peptides (Hayes et al. 2007), although bioactive peptides have been recently cataloged into as many as 37 identified activities based on the BIOPEP database, an in silico application for processing bioactive peptide sequences (Minkiewicz et al. 2008).

The aim of this article is to critically discuss new developments and applications of both bacteriocins and peptides in food research and how these developments impact food safety, quality, and nutrition/health, and ultimately consider how scientific findings are shaping the perceptions and future uses of these types of molecules.

FOOD SAFETY APPLICATIONS OF BACTERIOCINS AND PEPTIDES

Food processors run the risk of significant economic losses annually due to food spoilage resulting from microbial contamination. Although chemical preservatives may provide a solution, the use of such preservatives is generally frowned upon, as many, such as nitrite, can have negative consequences for human health. Moreover, the extent of problems associated with food safety as a result of microbial contamination appears to be alarmingly high. Indeed, in industrialized countries the percentage of the population suffering from foodborne disease each year has been reported to be up to 30% (World Health Organization 2007). Interestingly, the application of bacteriocins and peptides in foods has enormous potential to prolong shelf-life and increase food safety, thus eliminating or dramatically reducing the need for undesirable preservatives. Bacteriocins can be incorporated into the food matrix through three different routes: They may be added directly to foods as purified or semipurified antimicrobial additives (such as nisin through Nisaplin), or as bacteriocin-based ingredients from fermented foods (as observed for pediocin PA-1 through ALTA® 2351), or through bacteriocin-producing starter cultures (Schillinger et al. 1996). The application of bacteriocins in foods using such methods has been the topic of several extensive reviews (Castellano et al. 2008; De Vuyst & Leroy 2007; Deegan et al. 2006; Gálvez et al. 2007, 2008, 2010; Settanni & Corsetti 2008; Sobrino-López & Martín-Belloso 2008b). However, application of a bacteriocin alone in a food is unlikely to provide sufficient protection against microbial contamination (Deegan et al. 2006), which may have influenced the lack of enthusiasm for using such molecules in food preservation. But many recent studies have investigated the efficacy of using bacteriocins in conjunction with other preservation methods or hurdles and demonstrated very promising results (**Table 1**). Moreover, bacteriocins have greater opportunity to target Gram-negative pathogens if the outer membrane has been destabilized by the presence of another hurdle such as a chelating agent (Deegan et al. 2006, Stevens et al. 1991). More than 60 potential hurdles for food preservation have already been described (Leistner 1999), and in this respect bacteriocins have received much attention (Chen & Hoover 2003, Deegan et al. 2006, Gálvez et al. 2007, Ross et al. 2003). Hurdle technology is especially attractive in exploiting bacteriocins, as some peptides have demonstrated additive or synergistic effects when used in conjunction with other compounds or physical treatments and could provide an attractive approach to minimize the development of resistant strains (Gálvez et al. 2008). Organic acids can work well with bacteriocins as the increase in net charge of bacteriocins at low pH may facilitate bacteriocin translocation through the cell wall. In addition, the solubility of some bacteriocins may also be improved at low pH, facilitating diffusion (Gálvez et al. 2007). Chelating agents permeate the outer membrane of Gram-negative bacteria, thus enabling bacteriocins to reach the cytoplasmic membrane (Helander et al. 1997, Schved et al. 1994). Combining two or more bacteriocins has also provided promising results, particularly if the bacteriocins belong to different grouping schemes targeting different cellular components (Luders et al. 2003). Physical treatments have also been shown to potentiate bacteriocin activity. For example, the nonthermal treatment of high intensity pulsed electric field (HIPEF) can lead to microbial inactivation by the application of high voltage pulses (Vega-Mercado et al. 1997), damaging the bacterial membrane and thus complementing the mode of action of bacteriocins. The observed synergy between bacteriocins and high hydrostatic pressure (HHP) has also been hypothesized to be a result of cumulative damage to the cytoplasmic membrane (Gálvez et al. 2007). The use of antimicrobial cocktails that target different bacteria may also enhance the efficacy of high pressure treatments based on studies using nisin with lysozyme, lactoferricin, and a synthetic lysozyme-derived peptide (Masschalck et al. 2003).

Antimicrobial peptides derived from edible proteins have also exhibited inhibitory activity against food spoilage and pathogenic microorganisms, including *Escherichia coli*, *Listeria*,

Table 1 Examples of the application of bacteriocins with other hurdles

Bacteriocin(s)	Natural antimicrobial(s)	Target microorganism	Background	Reference
Bacteriocin combined with NaCl				
Enterocin AS-48 (10 μg ml^{-1})	NaCl (6 or 7%) 4°C	*Staphylococcus aureus*	Culture media	(Ananou et al. 2004)
Bacteriocin combined with nitrite				
Nisin (450 mg l^{-1})	Nitrite (180 mg l^{-1})	*Leuconostoc mesenteroides*	Broth	(Gill & Holley 2003)
		Listeria monocytogenes		
Enterocin EJ97 (1 [a]AU ml^{-1})	Nitrite (25–100 μg ml^{-1})	*Bacillus macroides* *Bacillus maroccanus*	Broth	(García et al. 2004a)
Enterocin EJ97 (20 AU ml^{-1})	Nitrite (25–100 μg ml^{-1})	*Listeria monocytogenes*	Broth	(García et al. 2004b)
Enterocin AS-48 (5 μg ml^{-1})	Nitrite (150 ppm)	*Bacillus cereus*	Broth	(Abriouel et al. 2002)
Bacteriocin combined with organic acids				
Nisin (120–180 [b]IU g^{-1})	Sodium lactate (18 g kg^{-1})	*Listeria monocytogenes*	Cold smoked rainbow trout	(Nykanen et al. 2000)
Pediocin (6,000 AU ml^{-1})	Sodium diacetate (3%) and sodium lactate (6%)	*Listeria monocytogenes*	Beef franks	(Uhart et al. 2004)
Nisin (50 μg ml^{-1})	Sodium lactate (2%) or Potassium sorbate (0.02%)	*Salmonella*	Fresh cut cantaloupe	(Ukuku & Fett 2004)
Lacticin 3147 (2,500 AU ml^{-1})	Sodium citrate (2%) or Sodium lactate (2%)	*Clostridium perfringens*	Fresh pork sausage	(Scannell et al. 2000b)
Enterocin AS-48 (8 or 16 μg ml^{-1})	Sodium lactate (0.5%–3%)	*Bacillus cereus*	Rice gruel	(Grande et al. 2006)
Bacteriocin combined with chelating agents				
Nisin (300 IU ml^{-1})	EDTA (20 mM)	*Escherichia coli* *Salmonella* spp. *Listeria monocytogenes*	Apple cider	(Ukuku et al. 2009)
Enterocin AS-48 (50 or 100 μg ml^{-1})	Sodium tripolyphosphate (0.5%)	*Escherichia coli* O157:H7	Apple juice	(Ananou et al. 2005)
Nisin (450 mg l^{-1})	EDTA (900 mg/l)	*Listeria monocytogenes*	Broth	(Gill & Holley 2003)
Enterocin EJ97 (1 AU ml^{-1})	Sodium tripolyphosphate (0.3 or 0.5%)	*Bacillus macroides* *Bacillus maroccanus*	Broth	(García et al. 2004a)

Bacteriocin combined with essential oils				
Nisin (0.625 μg ml^{-1})	Carvacrol (0.0075%) or Thymol (0.01%) or Eugenol (0.02%) All with diglycerol fatty acid ester–$DGMC_{12}$ (0.0025%)	*Listeria monocytogenes*	Broth	(Yamazaki et al. 2004)
Nisin Z (40 IU ml^{-1})	Thymol (0.02%)	*Listeria monocytogenes*	Broth	(Ettayebi et al. 2000)
Nisin Z (75 IU ml^{-1})	Thymol (0.03%)	*Bacillus subtilis*		
Nisin (25–200 ppm)	Cinnamon (0.3%)	*Salmonella typhimurium* *Escherichia coli* O157: H7	Apple juice	(Yuste & Fung 2004)
Enterocin AS-48 (80 μg ml^{-1})	Hydrocinnamic acid (20 mM) or Carvacrol (126 mM)	*Staphylococcus aureus*	Carbonara sauce	(Grande et al. 2007)
Enterocin AS-48 (30 μg g^{-1})	Various essential oils at 1%	*Listeria monocytogenes*	Ready-to-eat salad	(Molinos et al. 2009)
Nisin (500 or 1,000 IU g^{-1})	Thyme (0.6%)	*Listeria monocytogenes*	Minced beef	(Solomakos et al. 2008)
Bactericins combined with other bacteriocins, peptides, and proteins				
Enterocin AS-48 (30 μg g^{-1})	Nisaplin (0.25% or 0.5%)	*Listeria monocytogenes*	Ready-to-eat salad	(Molinos et al. 2009)
Nisin (0.25 μM)	α_{s2}-casein f^{c} (183–207)	*Listeria monocytogenes*	Broth	(Lopez-Exposito et al. 2008)
Nisin (50–1,000 ^{d}BU ml^{-1})	Pediocin (50–1,000 BU ml^{-1})	*Bacillus spores*	Sous vide products	(Cabo et al. 2009)
Nisin (10 or 100 IU ml^{-1})	Lactoperoxidase (0.2 or 0.8 U ml^{-1})	*Listeria monocytogenes*	UHT skim milk	(Zapico et al. 1998)
Nisin (50 IU ml^{-1})	Curvaticin 13 (160 AU ml^{-1})	*Listeria monocytogenes*	Broth	(Bouttefroy & Milliere 2000)
Nisin	Lysozyme	*Lactobacillus curvatus* *Staphylococcus aureus*	Broth or pork juice	(Chung & Hancock 2000)
Pediocin PA-1 or Sakacin P or (64–128 μg ml) Curvacin A	Eukaryotic antimicrobial peptide pleurocidin (16 μg ml^{-1})	*Escherichia coli*	Broth	(Luders et al. 2003)

(*Continued*)

Table 1 (*Continued*)

Bacteriocin(s)	Natural antimicrobial(s)	Target microorganism	Background	Reference
Bactericins combined with high pressure treatments				
Nisin (500 IU ml^{-1}) Nisin (500 IU ml^{-1}) Nisin (500 IU ml^{-1}) Nisin (500 IU ml^{-1})	500 MPa (5 min) 500 MPa (5 min) 400 MPa (5 min) 250 MPa (5 min	*Listeria innocua* *Lactobacillus viridescens* *Escherichia coli* *Pseudomonas fluorescens*	Milk	(Black et al. 2005)
Nisin (10 IU ml^{-1})	250 MPa	*Listeria innocua*	Apple juice Carrot juice	(Pathanibul et al. 2009)
Nisin (1%)	250 MPa (30 min)	*Salmonella enteriditis*	Saline	(Ogihara et al. 2009)
Lacticin 3147 (10,000 AU ml^{-1}) Lacticin 3147 (15,000 AU ml^{-1})	250 MPa (30 min) 275 MPa (30 min)	*Staphylococcus aureus* *Listeria innocua*	RSM Whey	(Morgan et al. 2000)
Bactericins combined with high-intensity pulsed-electric field (HIPEF)				
Nisin (20 IU ml^{-1}) & Enterocin AS-48 (28 arbitary units ml^{-1})	HIPEF (800 μs)	*Staphylococcus aureus*	Milk	(Sobrino-Lopez et al. 2009)
Enterocin AS-48 (2.0 μg ml^{-1})	HIPEF (1000 μs)	*Lactobacillus diolivorans*	Apple juice	(Martínez Viedma et al. 2009)
Nisin (300 IU ml^{-1})	HIPEF (1200 μs)	*Staphylococcus aureus*	Milk	(Sobrino-Lopez & Martin-Belloso 2008a)
Bactericins combined with other treatments				
Gassericin A (49 arbitary units ml^{-1})	Glycine (0.5%)	*Bacillus cereus* *Lactococcus lactis*	Custard	(Arakawa et al. 2009)
Nisin (25 mg ml^{-1})	Diacetyl (2.5 mm L^{-1})	*Enterobacter sakazakii*	Broth	(Lee & Jin 2008)
Nisin (100 IU ml^{-1})	Microgard^{TM} (5%)	*Listeria innocua*	Liquid cheese whey	(von Staszewski & Jagus 2008)
Nisaplin (0.5%)	Pulsed Light (10.1 J cm^{-2})	*Listeria innocua*	Ready-to-eat sausages	(Uesugi & Moraru 2009)
Divergicin M35 (0.125 mg ml^{-1})	Chitosan-2 kDa (1.25 mg ml^{-1}) Chitosan-20 kDa (1.25 mg ml^{-1}) Chitosan-100 kDa (0.3125 mg ml)	*Listeria monocytogenes*	Broth	(Benabbou et al. 2009)

[a]AU = activity units, [b]IU = international units, [c]f = fragment, [d]BU = bacteriocin units.

Salmonella, *S. aureus*, *Bacillus* species, yeasts, and filamentous fungi. Milk-derived antimicrobial peptides, including bovine-derived lactoferricins, human lactoferrin, and casein-derived antimicrobial peptides, have attracted the most attention in recent years (López-Expósito & Recio 2008). For example, enzymatic hydrolysis of bovine lactoferrin resulted in the generation of peptides able to inhibit the wine spoilage yeast *Dekkera bruxellenis* and LAB known to cause spoilage during the wine-making process (Enrique et al. 2008, 2009). Casein-derived antimicrobial peptides resulting after fermentation demonstrated antibacterial activity against the pathogenic strains *E. coli* and *Enterobacter sakazakii*, the latter of which can be problematic in milk-based infant formulas (Hayes et al. 2006). More recently, antimicrobial peptides were isolated from three commercial Cheddar cheese samples which exhibited activity against *Bacillus cereus* and *E. coli*. The most biologically active peptides were greater than 10 kDa in size (Pritchard et al. 2010). Interestingly, synergistic effects have also been reported for combinations of antimicrobial peptides and bacteriocins. Combining nisin with αs2-casein (f)(183–207) demonstrated synergistic antimicrobial activity against the food pathogen *L. monocytogenes* (López-Expósito et al. 2008). Moreover, combining any of three LAB bacteriocins, pediocin PA-1, sakacin P, and curvacin A, with 2 μg of the eukaryotic peptide pleurocidin resulted in complete inhibition of *E. coli* growth, which was not possible using any of the antimicrobial treatments alone (Luders et al. 2003).

Bacteriocin Bioengineering Strategies for Increased Efficacy

Bacteriocin bioengineering can be exploited to improve bacteriocin solubility and stability, increase the spectrum of bacteriocin inhibition, and enhance antimicrobial activity. The gene-encoded nature of bacteriocins renders these antimicrobial molecules ideal candidates for bioengineering strategies. Novel bacteriocins can be generated by either mutating bacteriocin-encoding genes or by fusing genes from different bacterial species (Gillor et al. 2005). For example, the solubility of nisin Z at neutral pH was markedly improved by replacing asparagine at position 27 and histidine at position 31 with lysine residues using site-directed mutagenesis (Rollema et al. 1995). Moreover, replacement of dehydroalanine at position 5 with dehydrobutyrine resulted in a mutant with lower activity but which was significantly more resistant to acid-catalyzed chemical degradation compared with the natural derivative. A more recent study demonstrated that various activities of nisin can be engineered independently (Rink et al. 2007). For example, mutation of ring A within the peptide results in variants with enhanced activity and a modulated spectrum of activity against target cells. C-terminally truncated nisin A mutants lacking rings D and E retain significant antimicrobial activity but are unable to permeabilize the target membrane, and the opening of ring B eliminates antimicrobial activity but retains autoinducing activity. Random mutagenesis was recently used to generate the largest bank of randomly mutated nisin derivatives reported to date (Field et al. 2008). This led to identification of a nisin-producing mutant with enhanced activity against the mastitic pathogen *Streptococcus agalactiae* as a result of an amino acid change in the hinge region. Based on this discovery, mutants were generated with enhanced antimicrobial activity against *L. monocytogenes* and *S. aureus* using site-directed and site-saturation mutagenesis of the hinge region residues of the peptide (**Figure 1**).

Microcin J25 is produced by *E. coli* and is active against several human pathogens including *Salmonella* spp., *Shigella* spp., and *E. coli*, including *E. coli* 0157: H7 (Blond et al. 1999, Sable et al. 2000, Salomon & Farias 1992). Its resistance to proteolytic enzymes present in the stomach limits its potential use as a food biopreservative, as it can affect the normal intestinal microbiota of the host when ingested. Substitution of glycine at position 12 with tyrosine resulted in the generation of a chymotrypsin-sensitive microcin J25 derivative, which retained almost full activity and inhibited the growth of *Salmonella enterica* serovar Newport and *E. coli* 0157: H7 in skim milk and egg yolk,

and this derivative was inactivated by digestive enzymes both in vitro and in vivo (Pomares et al. 2009). An improved version of the class IIa bacteriocin pediocin PA-1 was generated by fusing the C-terminal half of pediocin with the N-terminal half of enterocin A, which showed increased activity against a strain of *Leuconostoc lactis* isolated from sour-spoiled dairy product (Tominaga & Hatakeyama 2007). Moreover, shuffling four specific regions within the N-terminal half of pediocin PA-1 with the corresponding sequences from 10 other class IIa bacteriocins through a DNA-shuffling library resulted in active mutants with higher activity than the parental molecule, suggesting that DNA-shuffled bacteriocins could prove useful for inhibiting sour spoilage of dairy products (Tominaga & Hatakeyama 2007).

Although this type of technology has the potential to generate a limitless supply of potent naturally-derived food preservatives, consumer resistance to genetic engineering and restrictive legislation will undoubtedly limit its development and applications in the near future. However, as knowledge regarding genetically modified organisms expands beyond the scientific community and consumer demands for minimally processed foods increase, it is likely that engineered bacteriocins may enjoy a lucrative future in food safety.

Innovative Methods for Exploiting Food Safety Peptides and Bacteriocins in Foods

In many instances, peptides that exhibit effective antimicrobial activity in vitro fail to yield similar activities in vivo. For example, Enrique et al. (2007) observed that the efficacy of synthetic antimicrobial peptides was reduced when acting in wine, suggesting that the food matrix is an important consideration for the practical application of antimicrobial peptides. Many studies have demonstrated that food components can decrease the antimicrobial activity of nisin owing to proteolytic degradation (Bhatti et al. 2004, Chollet et al. 2008, Jung et al. 1992) or to binding of the peptide to fat or protein surfaces, resulting in reduced accessibility to bacterial cells (Laridi et al. 2003). Food packaging and peptide carrier systems offer innovative opportunities to exploit the full potential of antimicrobial peptides for food safety purposes. Although traditional food packaging provides mechanical support and protection from external influences and should have minimum interaction with food, antimicrobial/bioactive packaging deliberately interacts with the food or food environment (Dainelli et al. 2008), retarding microbial surface growth and extending shelf-life and promoting safety (Appendini & Hotchkiss 2002). The antimicrobial agents can be incorporated directly into polymers, can be coated or adsorbed onto polymer surfaces, or can be immobilized to polymers by ion or covalent linkages (Appendini & Hotchkiss 2002). However, the mode of activity of the antimicrobial agents is an important factor. Bacteriocins are ideal for incorporation into antimicrobial packaging because they interact with the external surface of the microorganism (cell wall and membrane) and do not have to be internalized to exhibit an effect. For example, immobilization of nisin onto polyethylene/polyamide pouches [at a concentration of 7,860 activity units (AU) cm^{-2}], which were used to package young Cheddar cheeses, deliberately inoculated on the surface with *Listeria innocua* reduced *L. innocua* levels by two logs when stored at 4°C over a 12-week period (Scannell et al. 2000a). Likewise, cellulose-based bioactive inserts impregnated with nisin (7,650 AU cm^{-2}) reduced levels of *Listeria* by $\geq$2 logs and *S. aureus* by $\sim$1.5 logs when interleaved between the slices of ham or cheese over a 24-day period at 4°C (Scannell et al. 2000a). Interestingly, lacticin 3147 did not adsorb to the plastic used in this study, which may be related to its two-component nature, requiring adsorption of both components for activity or interference with other proteins in the lacticin 3147 preparation (Scannell et al. 2000a). Nisin-coated polyethylene films (generated from a stock solution of nisin at a concentration of 6,400 AU ml^{-1}) were found to be effective at inhibiting *Micrococcus luteus* in broth and the bacterial

flora in milk, resulting in a reduction of 0.9 logs in raw milk and a 1.3-log reduction in pasteurized milk stored at 4°C for seven days (Mauriello et al. 2005). Although nisin release from the films was unpredictable, it was favored by low pH and high temperature. Biodegradable polylactic acid polymer films incorporated with nisin (0.04 mg cm^{-2} of film) significantly inhibited *L. monocytogenes* in culture medium and liquid egg white, reduced the cell population of *E. coli* 0157:H7 in orange juice, and reduced *Salmonella enteriditis* levels in liquid egg white (Jin & Zhang 2008). Cellulose acetate films containing pediocin from ALTA® 2351 interleaved between slices of ham reduced *Listeria* numbers by 2 logs after 15 days of storage at 12°C (Santiago-Silva et al. 2009). Nisin incorporated into sorbitol-plasticized sodium caseinate films at 1,000 international units (IU) cm^{-2} resulted in a reduction of 1.1 log CFU g^{-1} in *L. innocua* counts on surface-inoculated cheese. However, the antimicrobial effectiveness was found to be dependent on the distance from the contact surface on the films containing nisin to the cheese matrix, as observed for deep *Listeria*-inoculated cheese (Cao-Hoang et al. 2010). Combining nisin with other compounds or treatments in antimicrobial films has also provided promising results. Edible films manufactured with malic acid and nisin exhibited higher antilisterial activity than using malic acid alone (Pintado et al. 2009). Edible soy protein isolate films containing grape fruit seed extract (1% w/w), nisin (10,000 IU g^{-1}), and ethylenediaminetetraacetic acid (EDTA) (0.16% w/w) were able to reduce populations of *E. coli* 0157: H7, *Salmonella typhimurium* and *L. monocytogenes* and may have applications in various food products (Sivarooban et al. 2008). Ionizing radiation in combination with pectin films containing 0.025% nisin provided promising results for reducing *L. monocytogenes* growth in ready-to-eat turkey meat samples after one week at 10°C (Jin et al. 2009). Enterocin-activated coatings have also demonstrated good antilisterial activity (Iseppi et al. 2008, Marcos et al. 2007). Moreover, EDTA was shown to enhance the activity of enterocin EJ97 in coated polyethylene films against *Bacillus coagulans* (Martínez Viedma et al. 2010). Controlled release of nisin was achieved using multilayer films with hydrophobic and hydrophilic layers composed of ethylcellulose/hydroxypropylmethylcellulose/ethylcellulose (EC/HPMC/EC) (Guiga et al. 2010). Indeed, nisin from two-layer films (EC/HPMC) totally desorbed within 0.5 h, whereas the three-layer films (EC/HPMC/EC) expanded the nisin release time over 20 h and showed significant antimicrobial activity. Controlled release of the antimicrobial agent could be highly advantageous, ensuring that a constant level of antimicrobial agent reaches the food surface. It can also eliminate the risk of inactivation of the preservative by food components or dilution below the active concentration due to migration into the bulk food matrix (Appendini & Hotchkiss 2002). Atomic force microscopy (AFM) has recently been used to study bacteriocin distribution on coated polyethylene films (La Storia et al. 2008). Interestingly, antimicrobial distribution differed between bacteriocins, whereby nisin displayed a sort of microtexturing giving the highest roughness values, whereas the bacteriocin Bac162W displayed the most homogenous distribution, suggesting that this is an area that could be further optimized by enhanced understanding of bacteriocin interactions with various films.

Although active packaging is already in use in the United States, Japan, and Australia, its use in Europe has been limited mainly because of legislative restrictions (de Kruijf & van Beest 2003). However, new rules and guidelines on the topic were introduced across Europe in 2009. Within these regulations substances not previously assessed by the European Food Safety Authority (EFSA) will likely require a migration study followed by a basic set of toxicology tests before acceptance for use in active packaging (Harrington 2010). Antimicrobials in food packaging that may migrate to food are considered food additives and must meet the food additives standards (Appendini & Hotchkiss 2002). Given that nisin is already recognized as a food additive, nisin-activated packaging is most likely to appear on European supermarket shelves in the near future.

Several studies have developed methods to protect the antimicrobials within the food matrix itself, thus enhancing stability and effectiveness. Liposomes are vesicles composed of one or more phospholipid bilayers encapsulating a volume of aqueous media (da Silva Malheiros et al. 2010a) and have gained much attention for their ability to encapsulate and protect nisin (da Silva Malheiros et al. 2010b). Manufacture of liposomes requires input of energy (e.g., in the form of sonication, homogenization, shaking, heating, etc.), resulting in the arrangement of the lipid molecules in the form of bilayered vesicles, achieving a thermodynamic equilibrium in the aqueous phase (Mozafari 2005). Production of such vesicles containing antimicrobials, however, requires selection of suitable lipid-antimicrobial combinations (Were et al. 2003). Laridi et al. (2003) encapsulated nisin Z (a natural variant of nisin A) in commercial preparations of proliposomes that were able to withstand the Cheddar cheese–making temperature cycle and did not appear to disturb the fermentation process. Encapsulated nisin in phosphatidylcholine (PC) and PC-cholesterol was shown to inhibit growth of *L. monocytogenes* growth by >2 logs compared with free nisin (Were et al. 2004). More recently, microencapsulated nisin in nanovesicles prepared from partially purified soy lecithin was shown to be as effective as free nisin at inhibiting *L. monocytogenes* growth in whole and skim milk at low temperatures over 14 days (da Silva Malheiros et al. 2010b). Encapsulation of a bacteriocin-like substance (BLS) from *Bacillus licheniformis* in phosphotadylcholine vesicles completely inhibited the growth of *L. monocytogenes* and the encapsulated BLS was stable for up to 30 days at 4°C compared to only 14 days for the free bacteriocin (Teixeira et al. 2008).

More recently, bacteriocin-silicate interactions were studied as an alternative method for bacteriocin purification and subsequent delivery into food (Ibarguren et al. 2010). Bacteriocin produced by *Enterococcus faecium* was adsorbed from a bacteriocin solution by the inert silicates zeosil (synthetic silicate) and expanded perlite (natural compound), which are authorized as food-grade anticaking, clarifying, or filtering agents. The adsorbed bacteriocin retained its antimicrobial activity, reducing *Listeria* growth by 2 logs (zeosil-adsorbed bacteriocin) and 6 logs (expanded perlite-adsorbed bacteriocin). Food-grade silicates could provide a viable solution for preparation and purification of bacteriocins for industrial-scale use.

FOOD QUALITY APPLICATIONS OF BACTERIOCINS AND PEPTIDES

An open-ended interview assessing consumers' perception of which factors are important for quality food products radiated around four major quality dimensions: taste, health, convenience, and process characteristics (Brunsø et al. 2002), with taste as the most influential factor determining consumer choice (Glanz et al. 1998). Humans are capable of sensing five basic tastes, namely, sweet, umami, bitter, sour, and salt. Interestingly, peptides play a significant role in food taste. For example, a chicken protein hydrolysate resulted in the production of six peptides (di- and tripeptides) that were found to enhance the umami taste of inosine monophosphate (Maehashi et al. 1999). A synthetic peptide previously found in meat, termed BMP, was shown to enhance the flavor of beef gravy very similar to monosodium glutamate (MSG), but did not present the salty taste associated with MSG (Spanier et al. 1995). Several acidic oligopeptides isolated from fish protein hydrolysate have also demonstrated MSG-like flavor qualities (Noguchi et al. 1975). Three peptides isolated from cooked pork loins were found to have a sourness-suppressing effect (Okumura et al. 2004). A Maillard-reaction peptide resulting from the enzymatic hydrolysis of soybean protein was found to produce an enhanced effect on flavor, including umami, continuity, and mouthfulness in consommé soup (Ogasawara et al. 2006).

Although the above examples represent peptides that exhibit savory and palatable tastes, partial degradation of protein due to abnormal proteolysis can generate bitter peptides and

decrease the sensory quality of products (Maehashi & Huang 2009). Indeed, the formation of bitter peptides can be a major limitation in the exploitation of food protein hydrolysates (Saha & Hayashi 2001). Casein has been reported to produce the bitterest hydrolysates (Limieux & Suimard 1992, Minamiura et al. 1972), explaining the bitter taste associated with some cheese. Interestingly, significant correlations between increased angiotensin I–converting enzyme (ACE) inhibition and bitterness were also shown for casein-derived dipeptides based on experimental observations and quantitative structure-activity relationship (QSAR) models (Pripp & Ardo 2007). Both the peptide size and the presence of hydrophobic residues have been hypothesized as the main factors affecting the bitter taste of peptides (Maehashi & Huang 2009, Pripp et al. 2005). Of the 30 G protein–coupled taste receptors identified in humans, 25 are predicted to sense bitter tastes alone. Bitter molecules bind to the G protein–coupled receptor-type T2R on the apical membrane of the taste receptor cells located in the taste buds (Ley 2008). Most recently, the bitter taste receptor TR21 was shown to be activated by bitter-tasting dipeptides and tripeptides (Upadhyaya et al. 2010). Although several bitter-masking compounds have been identified, the majority have not been published in peer-reviewed journals but as patent applications (reviewed by Ley 2008). Interestingly, various acidic dipeptides containing asparaginic acid have demonstrated bitter-masking abilities (Fuller & Kurtz 1997, Harada & Kamada 2000).

Bacteriocins have also been used to improve the flavor and quality attributes of fermented foods. This has been achieved by using bacteriocin-producing LAB to control adventitious microbial populations, i.e., nonstarter lactic acid bacteria (NSLAB) (Ryan et al. 1996), and secondly by using bacteriocin-producing LAB as cell lysis–inducing agents to increase the rate of proteolysis in cheese (Morgan et al. 1997, O'Sullivan et al. 2002). NSLAB are responsible for defects such as the formation of calcium lactate crystals, slit formation, and off-flavor development, although they may also yield positive effects on flavor (Deegan et al. 2006). Based on such strategies, the NSLAB population of low-fat Cheddar cheese was successfully controlled during ripening using a lacticin 3147-producing transconjugant starter culture (Fenelon et al. 1999). A three-strain starter system consisting of a lactococcin A, B, and M producer (narrow-spectrum bacteriocins) resulted in the production of a cheese with decreased bitterness compared with cheese manufactured without the bacteriocin-producing adjunct as a result of bacteriocin-induced starter cell lysis during cheese manufacture and ripening (Morgan et al. 2002). A lacticin 481–producing adjunct culture was also shown to control NSLAB and accelerate starter cell lysis without compromising acid production of the starter (O'Sullivan et al. 2003). Enhanced lysis of adjunct cultures via a lacticin 3147–producing culture resulted in a concomitant increase in isoleucine transamination and about a twofold increase of the derived volatile compound 2-methylbutanal, resulting in an enhancement of the cheese aroma (Fernandez de Palencia et al. 2004). Using a similar concept, Danisco developed a freeze-dried culture of *Pediococcus acidilactici*, which is marketed as CHOOZIT™ Flav 43 and is suggested for use in Cheddar cheese and semihard cheeses as an adjunct that "accelerates and enhances strong and sweet flavour compounds, due to the production of bacteriocins." (**http://www.orchard-dairy.co.uk/downloads%5CChoozitFlavourAdjuncts_20022009102925.pdf**)

PEPTIDES IN NUTRITION AND HEALTH

Remarkably, through the years science has demonstrated that food can provide benefits to human health beyond just basic nutrition. Among the food constituents contributing to this effect are food-derived biologically active peptides that exhibit their effect through activity on eukaryotic cells. Indeed, several such peptides have been identified that are of plant and animal origin (**Table 2**). However, bovine milk, cheese, and dairy products have been reported to provide the greatest sources of bioactive proteins and peptides from food (Möller et al. 2008). These peptides may be

Table 2 Examples of food-derived sources of bioactive peptides

Source	Reference	Source	Reference
ACE inhibitory		**Antioxidant**	
Milk: β-casein, α_s1-casein, κ-casein, β-lactoglobulin, α-lactoglobulin	(FitzGerald et al. 2004) (Gobbetti et al. 2002) (Otte et al. 2007) (Hernández-Ledesma et al. 2007a) (Silva et al. 2006) (Hernández-Ledesma et al. 2007b) (Mao et al. 2007) (Chatterton et al. 2006)	Venison protein hydrolysate Wheat germ protein hydrolysate Milk Mackerel hydrolysate Soy hydrolysate Egg yolk hydrolysate Porcine collagen hydrolysate	(Kim et al. 2009) (Zhu et al. 2006) (Hogan et al. 2009) (Wu et al. 2003) (Gibbs et al. 2004) (Sakanaka et al. 2004) (Li et al. 2007)
Pork meat	(Escudero et al. 2010)	Canola protein hydrolysate	(Cumby et al. 2008)
Pacific hake fish hydrolysate	(Samaranayaka et al. 2010)	**Immunomodulatory**	
Sardine peptide	(Otani et al. 2009)	Whey protein hydrolysate	(Gauthier et al. 2006)
Antartic krill tail meat hydrolysate	(Hatanaka et al. 2009)	Salmon hydrolysate	(Yang et al. 2009)
Oat protein hydrolysate	(Cheung et al. 2009)	Soy hydrolysate	(Maruyama et al. 2003)
Corn gluten meal hydrolysate	(Yang et al. 2007)	Egg yolk peptides	(Nelson et al. 2007)
Royal jelly hydrolysate	(Takaki-Doi et al. 2009)	**Anticancer**	
Cooked eggs	(Majumder & Wu 2009)	Lunasin in soybean	(Hernández-Ledesma et al. 2009)
Egg white	(Miguel et al. 2007)	Soy proteins	(Kim et al. 2000)
Soybean	(Wu & Muir 2008)	Fish protein hydrolysate	(Picot et al. 2006)
Broccoli	(Lee et al. 2006)	Egg white hydrolysate	(Yi et al. 2003)
Chickpea legumin	(Yust et al. 2003)	Milk: lactoferricin	(Eliassen et al. 2002)
Sesame protein hydrolysate	(Nakano et al. 2006)	Ginseng	(Kim et al. 2003)
Buckwheat	(Ma et al. 2006)	Buckwheat	(Leung & Ng 2007)
Rice dreg hydrolysate	(He et al. 2005)	Chickpea protein hydrolysate	(Girón-Calle et al. 2010)
Hypocholesterolemic		**Antiobesity**	
Soy protein hydrolysates	(Zhong et al. 2007)	Soybean	(Nishi et al. 2003)
Milk: β-lactoglobulin	(Nagaoka et al. 2001)	Milk	(Aziz & Anderson 2003)
Fresh water clam hydrolysate	(Lin et al. 2010)	Fish protein hydrolysate	(Cudennec et al. 2008)
Anti-Thrombotic			
Milk: κ-casein	(Chabance et al. 1995)		
Pork	(Shimizu et al. 2009)		

released through the action of digestive enzymes in the intestine, chemical, or enzymatic hydrolysis in vitro, and via bacterial fermentation. Bioactive peptides may also be produced artificially via chemical synthesis, as well as through genetic engineering and biomanufacturing approaches (Shahidi & Zhong 2008).

Peptides offer huge potential in the development of functional food products by increasing their concentration in foods to a level that brings about a measureable biological effect or by introducing them into foods that are naturally free of them (De Leo et al. 2009). In this respect, bioactive peptides have become important constituents of several commercially available functional food products and ingredients (**Table 3**). In such products, the peptides are either added or enriched by modification of the usual manufacturing process (e.g., by changing the process parameters or

Table 3 Examples of commercially available functional foods or ingredients containing bioactive peptides[a]

Brand name	Product type	Health claim	Bioactive peptide	Manufacturer
Calpis	Sour milk	Reduction of blood pressure	VPP, IPP from β-casein and κ-casein	Calpis Co., Japan
Evolus	Fermented milk, calcium enriched	Reduction of blood pressure	VPP, IPP from β-casein and κ-casein	Valio, Finland
BioZate	Hydrolysed whey protein isolate	Reduction of blood pressure	Whey peptides	Davisco, USA
C12 Peption	Ingredient	Reduction of blood pressure	Casein-derived dodecapeptide FFVAPFPEVFGK	DMV, Netherlands
Peptide Soup	Soup	Reduction of blood pressure	Bonito-derived peptides	NIPPON, Japan
Casein DP Peptio Drink	Soft Drink	Reduction of blood pressure	Casein-derived dodecapeptide FFVAPFPEVFGK	Kanebo, Japan
BioPURE-GMP	Whey protein hydrolysate	Anticariogenic, Antimicrobial, Antithrombotic	Glycomacropeptide κ-casein f[b](106–169)	Davisco, USA
CholesteBlock	Drink powder	Hypocholesterolemic	Soy peptides bound to phospholipids	Kyowa Hakko, Japan
CSPHP ProDiet F200	Milk drink, confectionary	Reduce stress	α_{s1}-casein f(91–100) YLGYLEQLLR	Ingredia, France
Capolac	Ingredient	Helps mineral absorption	Caseinphosphopeptide	Arla Foods, Denmark
Tekkotsu Inryou	Soft drink	Helps mineral absorption	Caseinphosphopeptide	Suntory, Japan
Kotsu Kotsu calcium	Soft drink	Helps mineral absorption	Caseinphosphopeptide	Asahi, Japan
CE90CPP	Ingredient	Helps mineral absorption	Caseinphosphopeptide	DMV, Netherlands
Glutamine peptide	Dry milk protein hydrolysate	Immunomodulatory	Glutamine-rich peptides	DMV, Netherlands
Festivo	Fermented low-fat hard cheese	Reduction of blood pressure	α_{s1}-casein f(1–6) RPKHPI, f(1–7) RPKHPIK, f(1–9) RPKHPIKHQ	MTT Agrifood Research, Finland
Cysteine Peptide	Ingredient	Boost energy, improve sleep quality	Milk-derived peptide	DMV, Netherlands
PeptoPro	Ingredient	Improves athletic performance and muscle recovery	Casein-derived peptide	DSM, Netherlands
Vivinal Alpha	Ingredient	Aids relaxation and sleep	Whey-derived peptide	Borcula Domo Ingredients (BDI), Netherlands
Recaldent	Chewing gum	Anticariogenic	Caseinphosphopeptides	Cadbury Enterprises
Evolus Double Effect Spread	Margarine	Reduction of blood pressure	Milk-derived peptides	Valio, Finland

[a]Adapted and updated from Korhonen (2009), Korhonen & Pihlanto (2006), Hartmann & Meisel (2007).
[b]f = fragment.

the starter cultures used) (Hartmann & Meisel 2007). These peptides have the capacity to exert numerous health effects, as discussed below.

Peptides with Potential to Reduce the Risk of Cardiovascular Diseases

Cardiovascular diseases (CVDs) describe a group of disorders of the heart and blood vessels, and are the number one cause of death globally. Interestingly, several food-derived bioactive peptides have gained scientific interest as a result of their capacity to alleviate the risks associated with CVD. These include antihypertensive, antithrombotic, hypocholesterolemic, and antiobesity peptides (Erdmann et al. 2008).

Antihypertensive peptides. The antihypertensive peptides work by inhibiting a key enzyme involved in the regulation of BP, namely, ACE. These ACE inhibitors are thought to be competitive inhibitors of ACE by preventing ACE from synthesizing the potent vasoconstrictor, angiotensin II. In addition, ACE also hydrolyzes bradykinin, a vasodilator (Seppo et al. 2003). Peptides with ACE-inhibitory activity have been identified and studied from a range of food sources, including milk, egg, fish, soy, meat, sesame, broccoli, buckwheat, and rice (**Table 2**).

The ACE inhibitory peptides Val-Pro-Pro (Clare et al. 2003, Hamel et al. 1985, Juillard et al. 1995) and Ile-Pro-Pro (Chabance et al. 1995, Drouet et al. 1990) are derived from casein following bacterial fermentation and produced in the commercial fermented milk product, Calpis® (Calpis, Co. Ltd., Tokyo). Following oral consumption of 95 ml Calpis® over an 8-week period, a significant reduction in BP was obtained in mildly hypertensive patients (Hata et al. 1996). More recently, a spread containing Val-Pro-Pro and Ile-Pro-Pro and plant sterols was shown to have a beneficial effect on two major cardiovascular risk factors, BP and plasma lipids (Turpeinen et al. 2009). Remarkably, Val-Pro-Pro and Ile-Pro-Pro have the potential to inhibit ACE in a very similar fashion to the current synthetic ACE inhibitors Captopril, Enalaprilat, and Lisinopril by hydrogen bonding with similar residues in the ACE catalytic site (Pina & Roque 2008). Recombinant DNA technologies have now been exploited to produce antihypertensive peptides. Recombinant fusion proteins have been expressed in *E. coli* and are then purified and cleaved by proteinase from a selected strain of *Lactobacillus helveticus* (Losacco et al. 2007). This technology should enable scientists to generate designer peptides with stronger inhibitory activity and new therapeutic properties.

Antithrombotic peptides. Thrombosis is a pathological condition that results in clots or thrombus formation in arteries, veins, or the chambers in the heart. Interestingly, a significant amount of similarities exist between the mechanisms involved in milk clotting, defined by the interaction of κ-casein with chymosin and the mechanisms of blood clotting, defined by the interaction of fibrinogen with thrombin (Jolles 1975, Jolles & Henschen 1982, Rutherfurd & Gill 2000). Hence, some of the most antithrombotic peptides identified to date are derived from the enzymatic hydrolysis of bovine κ-casein. Indeed, having found structural similarities between bovine κ-casein and the human fibrinogen γ-chain, Jolles et al. (1978) hypothesized that both may have evolved from a common ancestor during the past 450 million years. The main antithrombotic peptide isolated from bovine κ-casein corresponding to f (106–116), with the amino acid sequence MAIPPKKNQDK termed casoplatelin, was also shown to inhibit ADP-induced platelet aggregation and fibrinogen binding in a concentration-dependant manner (Jolles et al. 1986). Interestingly, it is thought that milk protein–derived antithrombotic peptides are absorbed into the bloodstream. For example, two peptides from human and bovine κ-caseinoglycopeptide have

been identified in the plasma of five-day-old newborns following ingestion of a cow milk–based formula (Chabance et al. 1995).

Hypocholesterolemic peptides. Positive correlations have been observed between the risk of developing CVD and hypercholesterolemia and/or hypertriglyceridemia (Hokanson & Austin 1996, Martin et al. 1986). Peptides derived from dietary soy protein, as well as whey-derived peptides, have reported hypocholesterolemic properties. The exact mechanisms responsible for these effects are unclear. However, the soy glycinin peptides with amino acid sequences LYPR and IAVPGEVA have demonstrated cholesterol-lowering effects by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR), a key enzyme in cholesterol biosynthesis (Pak et al. 2005, Yoshikawa et al. 2000). The α′-subunit of soy β-conglycinin demonstrated plasma lipid–lowering properties and upregulation of liver β-very low density lipoprotein (VLDL) receptors in hypercholesterolemic rats following oral administration (Duranti et al. 2004). Various studies have demonstrated that milk whey protein has similar cholesterol-lowering effects to soy protein, which is more dramatic for the whey peptide fraction than the intact whey protein (Nagaoka 1996, Nagaoka et al. 1992). IIAEK (also called lactostatin) has been identified as the hypocholesterolemic peptide derived from β-lactoglobulin, which exhibited a greater cholesterol-lowering effect than β-sitosterol following oral administration in rats (Nagaoka et al. 2001). Recently, the activity of IIAEK was linked to the upregulation of a human cholesterol-metabolizing enzyme called cholesterol 7α-hydroxylase (CYP7A1) (Morikawa et al. 2007).

Peptides Associated With Satiety

Obesity is associated with numerous comorbidities, among which include CVD, type 2 diabetes, hypertension, certain cancers, and sleep apnea/sleep-disordered breathing (Poirier et al. 2006). Currently, weight loss programs have moved toward schedules favoring a decrease in energy intake while preserving the highest level of satiety possible (Tremblay et al. 2007). Many studies have speculated that peptides have the capacity to affect several satiety signals in the gut, with the result of preventing further food intake (Erdmann et al. 2008). Such satiety signals include opioid receptors, cholecystokinin (CCK)-A receptors, and the glucagon-like peptide (GLP)-1, whose roles in the regulation of appetite and food intake are well recognized (Druce & Bloom 2006). Peptides derived from soy and casein have been shown to induce satiety by the independent activation of both opioid and CCK-A receptors (Pupovac & Anderson 2002). The peptide VRIRLLQRFNKRS corresponding to f(51–63) of soy β-conglycinin was shown to be responsible for appetite suppression by stimulating CCK release in rats (Nishi et al. 2003). Opioid peptides called casomorphins released from casein via proteolysis have also been shown to slow gastric motility and prevent further food intake (Daniel et al. 1990). Peptides released from casein and whey have been linked to induction of satiety through the GLP-1 signaling pathway, resulting in suppression of food intake (Aziz & Anderson 2003, Hall et al. 2003). However, neither free amino acids nor intact proteins were capable of stimulating GLP-1 release (Cordier-Bussat et al. 1998).

Peptides and Immunomodulation

Peptides derived from various protein sources, including milk, egg, fish, and soy protein (**Table 2**), have demonstrated immunomodulatory effects ranging from the proliferation of lymphocytes, natural killer (NK) cell activity, antibody synthesis, and cytokine regulation (Gill et al. 2000, Horiguchi et al. 2005). For example, casein-derived immunopeptides have been shown to

stimulate the phagocytic activities of both human and murine macrophages and to protect against *Klebsiella pneumoniae* infection in mice (Smacchi & Gobetti 2000). Immunomodulatory peptides derived from rice and soybean were shown to stimulate superoxide anions [reactive oxygen species (ROS)], which trigger nonspecific immune defences (Kitts & Weiler 2003). Recently, lunasin, a 43 amino acid peptide from soybean, and lunasin-like peptides were shown to inhibit inflammation by suppressing NF-κB pathway (Gonzalez de Mejia & Dia 2009). Korhonen & Pihlanto (2003) have suggested that immunomodulatory peptides may alleviate allergic reactions in humans and enhance mucosal immunity in the gastrointestinal tract. The release of such peptides from hydrolyzed milk protein preparations may be responsible for the antiallergenic effects observed for protein hydrolysate formulas also known as hypoallergenic formulas, which are used in many infant formulations for infants suffering from cow's milk allergy.

Mineral-Binding Peptides

Mineral-binding peptides such as the CPPs are negatively charged and can efficiently bind divalent cations such as Fe, Mn, Cu, and Se, thereby improving their bioavailability. Several studies have investigated whether CPPs in the diet can increase calcium absorption, but the results are contradictory between human and animal studies (Scholz-Ahrens & Schrezenmeir 2000). For example, 1.0 mg of CPPs administered extrinsically by gastric intubation to young male rats dramatically increased calcium absorption from calcium-fortified milk compared to the control (Tsuchita et al. 2001). Most recently, the addition of CPPs was also shown to have a beneficial effect on the absorption of calcium from calcium fortified bovine and caprine milks in growing rats (Mora-Gutierrez et al. 2007). It was also demonstrated that CPPs induce the influx of calcium into human HT-29 cells (Ferraretto et al. 2001). However, administration of one gram of CPPs did not affect calcium metabolism acutely in nine postmenopausal women following administration of either CPP-enriched milk or CPP-enriched fermented milk (Narva et al. 2003). Although the effect of high doses of two well-defined CPP-enriched preparations on 15 volunteers consuming calcium lactate drinks did indicate a positive effect of the CPPs on calcium absorption, it was concluded that the differences in calcium absorption were unlikely to have any biological significance (Teucher et al. 2006). CPPs have also demonstrated anticariogenic properties and can prevent enamel demineralization (Aimutis 2004, Grenby et al. 2001). Most recently, a highly diluted CPP-amorphous calcium phosphate (CPP-ACP) preparation showed potential as a tooth-transport medium by preserving the viability of an L929 fibtoblastic cell line (Cehreli et al. 2008). CPPs are currently being used in commercial products for dental care (Cross et al. 2007, Luo & Wong 2007) (**Table 2**).

Peptides Exhibiting Anticancer Activities

Numerous peptides with reported anticancer activities have been identified in a variety of proteins including fish, egg, milk, soy, buckwheat, and ginseng (**Table 2**). For example, lunasin has demonstrated anticancer activity in mammalian cells and was found to inhibit the activity of skin carcinogens in mice (Hernández-Ledesma & de Lumen 2008). It has been suggested that the peptide exhibits this effect by inhibiting core histone acetylation, which can have considerable influence on the organization of chromatin and on the control of gene expression and cell growth (Grunstein 1997, Kuo & Allis 1998). Waste whey peptides from Mozzarella di Bufala Campana cheese were recently shown to exert a significant antiproliferative effect on a Caco-2 cell line (De Simone et al. 2008).

Antioxidant Peptides

Peptides exhibiting antioxidant activity exert their effect by preventing the enzymatic and nonenzymatic peroxidation of essential fatty acids and have been found in a variety of sources including milk, soy, egg yolk, porcine skin, fish, and canola, among others (**Table 2**). The exact mechanism responsible for antioxidant activity is unclear. However, Erdmann et al. (2006) demonstrated that the biofunctional peptide MY derived from sardine muscle stimulated expression of the antioxidant defense proteins heme oxygenase (HO)-1 and ferritin in endothelial cells, resulting in a sustained cellular protection from oxidative stress. Casein and casein-derived peptides were found to inhibit the enzyme lipoxygenase, which catalyzes the peroxidation of unsaturated fatty acids such as linoleic (Rival et al. 2001). The antioxidant activities of whey-derived peptides have been linked to the presence of cysteine-rich proteins, which promote the synthesis of the intracellular antioxidant, glutathione (Meisel 2005). Such activities may help to alleviate the symptoms of CVD, as oxidative stress is another significant factor in the initiation and progression of several vascular diseases (Erdmann et al. 2008). Saito et al. (2003) constructed two tripeptide libraries based on an antioxidative peptide isolated from a soybean protein hydrolysate. One was a library of 108 peptides containing either His or Tyr residues, and the other was a library of 114 peptides related to Pro-His-His. Interestingly, two Tyr-containing tripeptides showed higher activities than those of two His-containing tripeptides in the peroxidation of linoleic acid, and cysteine-containing tripeptides demonstrated strong peroxynitrite scavenging activity. Recently, a fraction from a milk protein hydrolysate termed Val-F3 demonstrated significantly reduced meat lipid peroxidation at a level of 200 $\mu g\ g^{-1}$ in the meat (Hogan et al. 2009). Thus, as well as having a potential role to play in general health, antioxidant peptides may also be useful agents for maintaining the quality and freshness of meat products by preventing oxidative rancidity, which leads to rancid flavor and odors.

Peptides Involved in the Regulation of the Gastrointestinal Tract

The casein-derived peptide opioid β-casomorphin-7 and another milk-derived peptide termed mammary-associated serum amyloid A3 (M-SAA3) may have a role in maintaining homeostasis in the gastrointestinal tract. M-SAA3 is highly abundant in the colostrum of mammals (McDonald et al. 2001). A conserved amino acid motif in the M-SAA3 protein has been shown to enhance mRNA expression from human instestinal cells of a specific mucin, MUC3, which interferes with enteropathogen adherence to epithelial cells (Larson et al. 2003). In a similar fashion, β-casomorphin-7 was shown to significantly contribute to mucin production from both rat and human intestinal mucin-producing cells using real time–PCR and ELISA studies (Zoghbi et al. 2006). Because intestinal mucins play a protective role in the gut, consumption of products containing β-casomorphin-7 and M-SAA3 could help to improve intestinal health by retarding pathogen adherence to the intestinal surface and potentially reducing the onset of intestinal infections.

Increasing Peptide Bioavailability in Foods: Biopharming

One major goal of scientific research in functional foods is to increase the bioavailability of bioactive peptides by introducing amino acid sequences into food proteins through genetic engineering approaches, namely biopharming. Rice seed has recently been reviewed as a vehicle for oral delivery of high concentrations of bioactive peptide sequences (Yang et al. 2008). Soybean protein has also been reported as a good model for such approaches because the protein content among soybean is the highest among major crops (Prak et al. 2006). However, modified proteins

must form the correct conformations; otherwise, misfolded proteins may be degraded by proteinases present in vacuoles and thus will not be able to accumulate as storage proteins (Prak et al. 2006). Matoba et al. (2001) introduced the potent antihypertensive peptide derived from ovalbumen, RPLKPW (novokinin), into β-conglycinin, one of the major storage proteins of soybean. β-conglycinin is composed of three subunits, α, α′, and β (Maruyama et al. 1998). Within the β-conglycin α′ subunit, three RPLKPW-like sequences (RPQHPE, RPRQPH, and RPHQPH) were changed to RPLKPW by site-directed mutagenesis and the modified protein was expressed in *E. coli*. After recovery and ion exchange chromatography, the RPLKPW peptide was released from the recombinant α′ subunit following trypsin and chymotrypsin digestion. The undigested RPLKPW-containing α′ subunit exerted a hypotensive effect on spontaneously hypertensive rats (SHRs) following oral administration of 10 mg kg^{-1} (Matoba et al. 2001). Optimizing the amino acid residues surrounding the three RPLKPW sites in the modified α′ subunit facilitated release by gastrointestinal proteases (Onishi et al. 2004). Moreover, introduction of a fourth RPLKPW, as well as an extension domain corresponding to residues 1–143 of the protein, resulted in a newly modified protein that had antihypertensive properties in SHRs at doses of 2.5 and 1.0 mg kg^{-1}, respectively, the latter of which is 1/2,000 that of ovalbumin (Onishi et al. 2004). More recently, the vector encoding the modified β-conglycin α′ subunit containing the four RPLKPW sequences was introduced into somatic embryos by whisker-mediated gene transformation to produce a transgenic soybean (Yamada et al. 2008). Protein extracted from the transgenic soybean reduced systolic BP after single oral administration in SHRs at a dose of 0.15 g kg^{-1}. Defatted flour from the transgenic soybean also reduced the systolic BP at a dose of 0.25 g kg^{-1}. Multiple repeats of the hypocholesterolemic peptide IIAEK, derived from bovine milk β-lactoglobulin, were introduced into the five variable regions of soybean proglycinin A1aB1b. When expressed in *E. coli*, large-scale production of a small peptide of fewer than 10 amino acids was accomplished (Prak et al. 2006, Prak & Utsumi 2009). LAB are also ideal candidates as carriers of bioactive peptide sequences, especially as these bacteria are food grade and inherent constituents of many fermented food products. Milk-derived bioactive peptides, namely the 11-residue antimicrobial peptide from bovine lactoferrin (BL-11) and the 12-residue hypotensive peptide from α_{s1}-casein, have been cloned in *Streptococcus thermophilus* using synthetic genes encoding each peptide (Renye & Somkuti 2008). Such strategies have the potential to augment the nutritional profile of crops, animal protein, and even food cultures. Given the vast range of health effects attributable to bioactive peptides, biopharming peptides could prove to be a worthwhile approach to promoting human health while keeping disease at bay through nutrition.

In Silico Methods for Identification of Bacteriocins and Peptides

Nowadays, the initial identification and analysis of bacteriocins and peptides are markedly more efficient thanks to computational tools and total genome sequencing, which together are providing a wealth of information regarding the global capabilities of living cells and biologically active molecules. Indeed, using conserved motifs through bioinformatic tools, scientists can rapidly mine genomes for specific genes and functional traits, or search within proteins for the presence of biologically active sequences. Searching for bacteriocins among the abundance of available microbial genomes has proven effective for the identification of novel bacteriocins and novel-producing strains with potential food safety applications. For example, complete genome sequencing and bioinformatic analysis of the alkaliphilic bacterium *Bacillus halodurans* C-125 revealed the presence of the genetic machinery involved in the production of a novel two-peptide lantibiotic designated haloduracin, which displayed antimicrobial activity against a wide range of Gram-positive bacteria (Lawton et al. 2007). Class II bacteriocins are generally synthesized as inactive prepeptides

containing a conserved leader sequence called the double-glycine (GG) motif (Dirix et al. 2004a). The leader sequence is cleaved off the prepeptide by a transporter belonging to the peptidase C39 family domain, which contains two conserved motifs called the cysteine and histidine motifs (Havarstein et al. 1995). Dirix et al. (2004b) screened 45 fully sequenced Gram-positive genomes for peptides containing a GG motif and for the peptidease C39 domain at the nucleotide level. Interestingly, the screening resulted in a total of 48 candidate peptides, 15 of which were bacteriocins and 10 of which were bacteriocin homologs. More than 40% of the identified peptide genes were either unannotated or had not yet been recognized as secreted peptides in the genome-sequencing projects. Of the 29 hits for peptidase C39 domains, one or more possible GG peptides were found within the 10 kb limit of the in silico search. A similar search of 120 Gram-negative genomes identified peptides that show structural similarity to bacteriocin and peptide pheromones of Gram-positive bacteria (Dirix et al. 2004a). However, the limited sequence homology associated with bacteriocin structural genes prompted the development of the Web-based bacteriocin genome mining tool, BAGEL (**http://bioinformatics.biol.rug.nl/websoftware/bagel**) (de Jong et al. 2006). BAGEL combines information on sequence motifs, characteristics, and functions of the proteins involved in the biosynthesis of putative bacteriocins with the genetic context of the encoding genes. BAGEL enabled the identification of one additional potential bacteriocin in the genome sequence of *Streptococcus pneumoniae* TIGR4, which showed similarity to bacteriocin PlnB of *Lactobacillus plantarum*. Screening publicly available microbial genomes for genes encoding LanM proteins, which are required for posttranslational modification of type 2 lantibiotics, resulted in the identification of 89 LanM homologs, of which 61 were located in strains not known to be lantibiotic producers (Begley et al. 2009). This led to the identification of the novel two-peptide lantibiotic lichenicidin produced by *B. licheniformis*, which exhibited activity against *L. monocytogenes*, methicillan-resistant *S. aureus* (MRSA), and vancomycin-resistant *Enterococcus* strains.

Computational tools also exist that enable the identification of alternative sources of bioactive peptides, as well as insight into potential biological activities, a topic that has been recently reviewed (Minkiewicz et al. 2008). The four major peptide sequence databases include BIOPEP (Minkiewicz et al. 2008), EROP (Zamyatnin et al. 2006), SwePep (Falth et al. 2006), and PepBank (Shtatland et al. 2007). EROP, SwePep, and PepBank focus mainly on endogenous peptides, whereas BIOPEP concentrates mainly on peptides of food origin (Minkiewicz et al. 2008). QSAR, a computational approach that quantitatively derives the activity of a compound based on its chemical structure, has also been successfully applied to peptide science for predicting inhibitory properties of milk-derived and synthetic peptides (Pripp 2005, Wu et al. 2006a,b), peptides associated with bitterness (Kim & Li-Chan 2006), and antimicrobial peptides (Mikut 2010).

CONCLUSION: OUTLOOK FOR THE FUTURE

Today, the enormous challenges set for food manufacturers for fresh, nutritious, unadulterated foods, with the added benefit of reducing the risk of illness, have driven scientists to explore innovative means to fulfill safety, quality, and nutritional demands. In this respect, it is no coincidence that peptides, whether they are produced by bacteria as bacteriocins or are encrypted in protein sequences as bioactive peptides, are at the forefront of this food revolution. However, despite the wealth of examples provided in this review, certain issues must still be resolved before food manufacturers and consumers alike can fully appreciate the positive attributes of both sets of molecules. Bioactive peptides, which have the potential to protect the consumer from a myriad of health problems, are part of a lucrative food and drinks market that appears to be expanding globally. Yet, a major challenge to food scientists and manufacturers alike is the development of feasible, industrial-scale processes for the production of foods with physiologically significant concentrations

of bioactive peptides to match their health claims. This bioavailability issue may be solved in the future through recombinant DNA approaches, which will result in the generation of designer foods with increased levels of bioactive sequences currently being studied in the laboratory. In addition, proteins and peptides in foods may be destroyed by gastrointestinal enzymes before they can even reach the site of activity. For example, Schmelzer et al. (2007) demonstrated that the release of known bioactive peptides is unlikely from β-casein following peptic digestion under simulated gastric conditions. Indeed, after 60 minutes of digestion only small proportions of the sequence were completely intact. Moreover, although the bioactivity of short-chain peptides may be preserved during the gastrointestinal transit, Roufik et al. (2006) demonstrated that long-chain bioactive peptides may require protection from gastrointestinal enzymes to prevent hydrolysis. One solution to this dilemma is to engineer peptides that are resistant to the action of gastrointestinal enzymes. Using just such an approach, O'Shea et al. (2010) engineered variants of the bacteriocin Salivaricin P, which were resistant to specific protease action but retained significant antimicrobial activity. Moreover, the biological activity of many of these peptides has only been proven in vitro or in animal models and must be proven in humans before they are deemed worthy of inclusion in foods.

The exploitation of bacteriocins in food systems, on the other hand, should follow a more direct route but is presumably hampered by a general lack of awareness regarding their potential role in food, and more significantly, restrictive food legislation for their approval and acceptance as food preservatives. Indeed, it is still surprising that despite the wealth of bacteriocins that have been explored in the laboratory for food safety applications, only nisin and pediocin PA-1 are commercially available. However, the unprecedented demands for organic and fresh produce sweeping the globe positions bacteriocins as forerunners in biopreservation technology.

Despite the hurdles that must yet be surmounted for the exploitation of bacteriocins and peptides in food systems, the innovations and developments discussed in this review provide a taste of future trends on supermarket shelves and suggest that the generation of sophisticated foods with an inherent intelligence for programming human health, as well as managing innate strategies for maintaining food safety and quality, is now closer to being a reality than ever before.

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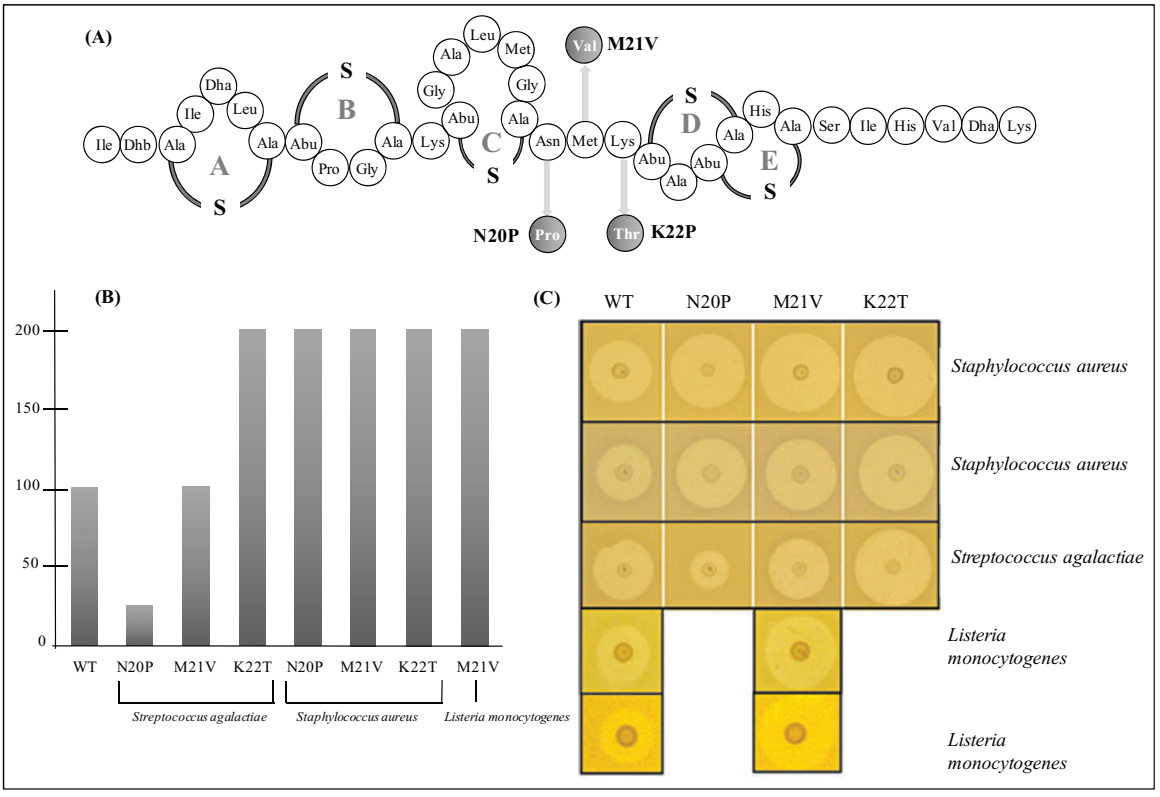

Figure 1

(*a*) Structure of nisin A; arrows indicate amino acid changes in mutant derivatives generated by genetic engineering. (*b*) Relative specific activity of purified nisin and nisin variants with wild-type (WT) nisin at 100%. (*c*) Growth inhibition of *Staphylococcus aureus* and *Streptococcus agalactiae* by N20P, M21V and K22T and of *Listeria monocytogenes* by M21V (from Field et al. 2008).

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Errata

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