

The dual role of bacteriocins as anti- and probiotics

O. Gillor · A. Etzion · M. A. Riley

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Abstract Bacteria employed in probiotic applications help to maintain or restore a host's natural microbial flora. The ability of probiotic bacteria to successfully outcompete undesired species is often due to, or enhanced by, the production of potent antimicrobial toxins. The most commonly encountered of these are bacteriocins, a large and functionally diverse family of antimicrobials found in all major lineages of Bacteria. Recent studies reveal that these proteinaceous toxins play a critical role in mediating competitive dynamics between bacterial strains and closely related species. The potential use of bacteriocin-producing strains as probiotic and bioprotective agents has recently received increased attention. This review will report on recent efforts involving the use of such strains, with a particular focus on emerging probiotic therapies for humans, livestock, and aquaculture.

Keywords Bacteriocin · Probiotic · Oral cavity · Gastrointestinal tract · Vagina · Livestock

Introduction

In 1908, Elie Metchnikoff, working at the Pasteur Institute, observed that a surprising number of people in Bulgaria lived more than 100 years (Metchnikoff 1908). This longevity could not be attributed to the impact of modern medicine because Bulgaria, one of the poorest countries in Europe at the time, had not yet benefited from such life-extending medical advances. Dr. Metchnikoff further observed that Bulgarian peasants consumed large quantities of yogurt. He subsequently isolated bacteria from the yogurt and determined that they conferred the observed health-promoting benefits (Metchnikoff 1908). Nearly a century elapsed before mainstream health providers considered using such bacteria to improve the health of their patients.

The term “probiotic,” which literally means “for life,” has since been employed to describe these health-promoting bacteria. The World Health Organization has defined probiotic bacteria as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (FAO/WHO 2001). Probiotic bacteria (PB) have been historically used to treat a variety of ailments, including infections of mucosal surfaces such as the vagina and the gastrointestinal (GI) tract. However, with the discovery and development of antibiotics in the twentieth century, the perceived value of these traditional therapies diminished (Bengmark 2001; Meier and Steuerwald 2005). Today, with the efficacy of antibiotics waning and a dramatic resurgence of infectious disease, physicians, researchers, and the public are reconsidering the possible role of probiotics as an

O. Gillor
Department of Environmental Hydrology & Microbiology,
Zuckerberg Institute for Water Research,
J. Blaustein Institutes for Desert Research,
Ben-Gurion University of the Negev,
Sde Boker Campus,
Beersheba 84990, Israel

A. Etzion
Department of Dryland Biotechnologies,
J. Blaustein Institutes for Desert Research,
Ben-Gurion University of the Negev,
Sde Boker Campus,
Beersheba 84990, Israel

M. A. Riley (✉)
Department of Biology, University of Massachusetts Amherst,
611 North Pleasant Street,
Amherst, MA 01003, USA
e-mail: riley@bio.umass.edu

alternative to supplement existing antibiotic-dominated therapies (Saavedra 2001; Senok et al. 2005). Over the past 15 years, there has been an increase in research on probiotic bacteria and a rapidly growing commercial interest in the use of probiotic bacteria in food, medicine, and as supplements (Morelli 2002; Scarpellini et al. 2008).

A variety of probiotic bacteria have been targeted as potential therapeutic agents. Examples include lactic acid bacteria (LAB; Carr et al. 2002), *Bifidobacteria* (Picard et al. 2005), *Saccharomyces* (Czerucka et al. 2007), enterics (Sartor 2003), and streptococci (Meurman and Stamatova 2007). Potential PB species differ in terms of their bioavailability, metabolic activity, and mode of action. However, to be used in host-associated activities, they all must be non-pathogenic and non-toxic. In addition, PB must survive the transition to the target niche and then persist, serving to protect the host against infection by pathogenic microorganisms (Klaenhammer and Kullen 1999).

Antimicrobial activity is thought to be an important means for PB to competitively exclude or inhibit invading bacteria (Carr et al. 2002; Roos and Holm 2002). Some do so by secreting non-specific antimicrobial substances, such as short-chain fatty acids (Carr et al. 2002) or hydrogen peroxide (Eschenbach et al. 1989), while others produce toxins with very narrow killing ranges, such as bacteriocins, bacteriocin-like inhibitory substances (BLIS), and bacteriophages (Smith et al. 2007; Tagg and Dierksen 2003).

Short-chain fatty acids such as formic, acetic, propionic, butyric, and lactic acids are produced during the anaerobic metabolism of carbohydrates and have an important role in decreasing pH. The microbial growth inhibition by organics may be due to the ability of these acids to pass across the cell membranes, dissociate in the more alkaline environment of the cells interior, and acidify the cytoplasm (Kashket 1987). Alternatively, the fermentation acid anion accumulation may cause osmotic stress (Diez-Gonzalez and Russell 1997). In microbial fermentor systems, a slight increase in the pH (5.5–6.5) resulted in a shift in the composition of the microbiota community from *Roseburia* and *Eubacterium rectale* at the lower pH to *Bacteroides* domination at the higher pH (Walker et al. 2005). These results indicate that *Bacteroides* species were able to outcompete other bacteria for the soluble carbohydrates, whereas at the lower pH, other bacterial groups were better able to compete for these substrates (Louis et al. 2007). The inhibition of another group, the enterobacteria, at acidic pH was already recognized as an important factor tending to limit the populations of certain gut pathogens (Diez-Gonzalez 2007). While production of short-chain fatty acids has been widely considered to be the main factor allowing lactic acid bacteria to dominate mucosal ecosystems, such as the vagina, more recent data suggest that

hydrogen peroxide production by lactobacilli species may be more relevant than acid production (Aslim and Kilic 2006; Kaewsrichan et al. 2006). Various *in vitro* and *in vivo* studies have shown that specific strains of lactobacilli inhibit the growth of bacterial species causing vaginal infection by producing hydrogen peroxide (Falagas et al. 2007).

Bacteriophages are highly specific and can be active against a single strain of bacteria. Therefore, using bacteriophage against infecting strains was suggested as a means to control undesirable bacterial species in mucosal systems (Joerger 2003). This approach was first developed early in the last century and showed much promise; however, it also aroused much controversy and concern. Consequently, recent studies investigating the *in vivo* use of bacteriophages are directed against pathogenic species infecting cattle and poultry (Andreatti Filho et al. 2007; Callaway et al. 2004).

Like bacteriophages, the bacteriocins can specifically target a particular subset of bacterial strains or species. However, unlike viruses, bacteriocins were found to be safe for human consumption by the Food and Drug Administration and have thus gained popularity in PB research. They are particularly attractive when the goal of PB application is to supplement, rather than dramatically alter, a host's natural bacterial flora. In this review, we explore what bacteriocins are and how one can co-opt the natural role bacteriocins serve in mediating strain and species interactions in the wild, to create highly effective PB strains.

The biology of bacteriocins

Bacteriocins were first identified almost 100 years ago as a heat-labile product present in cultures of *Escherichia coli* V and toxic to *E. coli* S and were given the name of colicin to identify the producing species (Gratia 1925). Fredericq demonstrated that colicins were proteins and that they had a limited range of activity due to the presence or absence of specific receptors on the surface of sensitive cells (Fredericq 1946). Since then, bacteriocins have been found in all major lineages of Bacteria and, more recently, have been described as universally produced by some members of the Archaea (Riley and Wertz 2002a; Riley and Wertz 2002b; Shand and Leyva 2008). According to Klaenhammer, 99% of all bacteria may make at least one bacteriocin, and the only reason we have not isolated more is that few researchers have looked for them (Klaenhammer 1988).

Two main features distinguish the majority of bacteriocins from classical antibiotics: bacteriocins are ribosomally synthesized and have a relatively narrow killing spectrum (Riley and Wertz 2002b). The bacteriocin family

includes a diversity of proteins in terms of size, microbial target, mode of action, release, and immunity mechanisms and can be divided into two main groups: those produced by Gram-negative and Gram-positive bacteria (Gordon et al. 2007; Heng et al. 2007).

Bacteriocins of Gram-negative bacteria

Recent surveys of *E. coli*, *Salmonella enterica*, *Hafnia alvei*, *Citrobacter freundii*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* reveal levels of bacteriocin production ranging from 3 to 26% of environmental isolates (Gordon et al. 2007; Riley et al. 2003). Colicins, bacteriocins produced by *E. coli*, are found in 30–50% of the strains isolated from human hosts and are often referred to as virulence factors (Riley and Gordon 1992). Much higher levels of bacteriocin production have been found in some Gram-negative bacteria, such as *Pseudomonas aeruginosa*, in which >90% of both environmental and clinical isolates produce bacteriocins (Michel-Briand and Baysse 2002).

Since their discovery, the colicins of *E. coli* have been the most extensively studied Gram-negative bacteriocins, and they now serve as a model system for investigating the mechanisms of bacteriocin structure/function, genetic organization, ecology, and evolution (Cascales et al. 2007). Colicins are high molecular weight proteins that kill target cells through a variety of mechanisms. Nomura showed that colicins E1 and K inhibit macromolecular synthesis without arrest of respiration, colicin E2 causes DNA breakdown, and colicin E3 stops protein synthesis (Nomura 1967). In each case, he showed that the lethal action is reversed by treatment with trypsin. Since his pioneering work, colicins were shown to kill their targets by either membrane permeabilization or nucleic acid degradation (Braun et al. 1994; Riley and Wertz 2002b; Smarda and Smajs 1998).

Colicins are usually encoded on one of two types of colicinogenic plasmids (Pugsley and Oudega 1987). Type A plasmids are small (6 to 10 kb) and present in numerous copies per cell. They are mobilizable in the presence of a conjugative plasmid and are amplifiable. Type B are monocopy plasmids of about 40 kb, which carry numerous genes in addition to those encoding colicin activity and are able to conjugate. However, plasmid carriage of bacteriocins is not a requirement. A close relative to the colicins, the bacteriocins of *Serratia marcescens*, are found on both plasmids and the chromosome (Ferrer et al. 1996; Guasch et al. 1995).

A colicin protein is comprised of three functionally distinct domains; receptor recognition, protein translocation, and killing (Cao and Klebba 2002). In colicins, the central domain comprises about 50% of the protein and is involved in the recognition of specific cell surface receptors

on the outer membrane of the target cell (Zakharov and Cramer 2004). The N-terminal domain (<25% of the protein) is responsible for translocation of the protein through the cell envelope by either the Tol or Ton machinery to its target (Zakharov and Cramer 2004; Zakharov et al. 2004), which is the inner membrane for ionophore colicins and the cytoplasm for nuclease colicins (James et al. 2002; Sharma et al. 2007). The remainder of the protein houses the killing domain and the immunity region, which is a short sequence involved in immunity protein binding (Cascales et al. 2007).

In addition to colicins, *E. coli* strains produce a second type of bacteriocin, known as microcins, which are smaller than colicins and share more properties with the bacteriocins produced by Gram-positive bacteria, including thermostability, resistance to some proteases, relative hydrophobicity, and resistance to extreme pH (Baquero and Moreno 1984; Gillor et al. 2004; Pons et al. 2002). Fourteen microcins have been reported to date, of which only seven have been isolated and fully characterized. However, these seven possess a diversity of killing mechanisms (Duquesne et al. 2007a); some are active as unmodified peptides, while others are heavily modified by dedicated maturation enzymes (Duquesne et al. 2007b; Severinov et al. 2007).

The successful use of probiotics-producing colicins, microcins, or any other bacteriocins requires understanding the factors influencing the frequency of bacteriocin production in a bacterial population. This aspect of bacteriocin ecology was recently studied in clinical and environmental *E. coli* populations. Recent evidence indicates that the frequency of bacteriocin production in *E. coli* populations can vary from 10 to 80% depending on the animal host from which they were isolated (Gordon et al. 1998; Gordon and O'Brien 2006), the host's diet (Barnes et al. 2007), temporal changes (Gordon et al. 1998), and the type of bacteriocin produced by the strain (Gordon et al. 2007). These observations suggest that it is not enough for antimicrobial-producing probiotics to be proven potent against pathogens; they also need to complement the existing bacterial dynamics in the target host.

Bacteriocins of Gram-positive bacteria

Bacteriocins of Gram-positive bacteria are as abundant and even more diverse than those found in Gram-negative bacteria. The Gram-positive bacteriocins resemble many of the antimicrobial peptides produced by eukaryotes; they are generally cationic, amphiphilic, membrane-permeabilizing peptides, and range in size from 2 to 6 kDa (Heng et al. 2007). They differ from bacteriocins of Gram-negative bacteria in two fundamental ways (Riley and Wertz 2002b). First, the bacteriocins produced by Gram-positive bacteria

are not necessarily lethal to the producing cell. This critical difference is due to dedicated transport mechanisms Gram-positive bacteria encode to release the bacteriocin toxin. Typically, their biosynthesis is self-regulated with specifically dedicated transport mechanisms facilitating release, although some employ the Sec-dependent export pathway (Drider et al. 2006; Eijsink et al. 2002; Maqueda et al. 2008). Second, the Gram-positive bacteria have evolved bacteriocin-specific regulation, whereas bacteriocins of Gram-negative bacteria rely solely on host regulatory networks (Nes et al. 1996).

Bacteriocins produced by LAB, which have a long history of use in fermentation and meat and milk preservation, are the best characterized of this group (Cintas et al. 2001). Four classes of LAB antibiotics are identified: Class I is comprised of modified bacteriocins, known as lantibiotics (Twomey et al. 2002); class II includes heat stable, minimally modified bacteriocins (Drider et al. 2006; Eijsink et al. 2002); class III includes larger, heat-labile bacteriocins; and class IV is comprised of complex bacteriocins carrying lipid or carbohydrate moieties (Heng et al. 2007). Classes I and II have been the focus of most probiotic research.

Lactic acid bacteria have been employed for centuries in the fermentation of food, partly due to the fact that they can prevent the growth of spoilage and pathogenic microorganisms (Cheigh and Pyun 2005). They produce bacteriocins, the lantibiotics, so named because they are post-translationally modified to contain amino acids such as thioether bridges of lanthionine and 3-methylanthionine or dehydroalanin (Twomey et al. 2002). Lantibiotics are ribosomally synthesized bacteriocins that target a broad range of Gram-positive bacteria and are subdivided into three groups on the basis of their structure and mode of action: type A lantibiotics, such as nisin, are small (2–5 kDa), elongated, screw-shaped proteins that contain positively charged molecules, which kill via the formation of pores, leading to the dissipation of membrane potential and the efflux of small metabolites from the sensitive cells (Nagao et al. 2006). Nisins have a dual mode of action: (1) They bind to lipid II, the main transporter of peptidoglycan subunits from the cytoplasm to the cell wall, and therefore prevent correct cell wall synthesis, leading to cell death, and (2) they employ lipid II as a docking molecule to initiate a process of membrane insertion and pore formation that leads to rapid cell death (Wiedemann et al. 2001). Type B lantibiotics, such as mersacidin (Twomey et al. 2002), kill by interfering with cellular enzymatic reactions, such as cell wall synthesis (Pag and Sahl 2002; Sahl and Bierbaum 1998; Sahl et al. 1995). Another subgroup is composed of two-component lantibiotics, such as lactacin 3147 (Wiedemann et al. 2006), consisting of two lantibiotic peptides that synergistically display antimicrobial activity (Ryan et al. 1998). It was shown that the dual

activities could be distributed across two peptides: While one resembles type B lantibiotic mersacidin, which depolarizes the membrane, the other is more similar to the type A lantibiotic class pore formers (Martin et al. 2004).

Class II LAB bacteriocins are also small nonlanthionine-containing peptides (Drider et al. 2006; Oppedgård et al. 2007). The majority of bacteriocins in this group kill by inducing membrane permeabilization and the subsequent leakage of molecules from target bacteria. These bacteriocins are organized into subgroups: Class IIa is the largest group and its members are distinguished by shared activity against *Listeria* and a conserved amino-terminal sequence (YGNGVXaaC) that is thought to facilitate nonspecific binding to the target surface. Like type A lantibiotics, class IIa bacteriocins act through the formation of pores in the cytoplasmic membrane. Examples include pediocin (this group is also called pediocin-like bacteriocins), sakacin A, and leucocin A (Drider et al. 2006; Hechard and Sahl 2002; Oppedgård et al. 2007). Class IIb bacteriocins such as lactacin F and lactococcin G form pores, composed of two different proteins, in the membrane of their target cells (Garneau et al. 2002; Hechard and Sahl 2002). A third subgroup (IIc) has been proposed, which consists of bacteriocins that are sec-dependent, such as acidocin 1B (Han et al. 2007). Class III bacteriocins are large heat-labile proteins such as helveticins J or lactacin B (Dobson et al. 2007; Joerger 2003). An additional proposed class (IV) requires lipid or carbohydrate moieties for activity. Little is known about the structure and function of this class. Examples include leuconocin S and lactocin 27 (Choi et al. 1999; Vermeiren et al. 2006).

Gram-positive bacteriocins, in general, and lantibiotics, in particular, require many more genes for their production than do those of Gram-negative bacteria (Nagao et al. 2006). The nisin gene cluster, for example, includes genes for the prepeptide (*nisA*), enzymes for modifying amino acids (*nisB*, *nisC*), cleavage of the leader peptide (*nisP*), secretion (*nisT*), immunity (*nisI*, *nisFEG*), and regulation of expression (*nisR*, *nisK*). These gene clusters are most often encoded on plasmids but are occasionally found on the chromosome (Cheigh and Pyun 2005). Several Gram-positive bacteriocins, including nisin, are located on transposons (Kim and Dunn 1997).

The conventional wisdom about the killing range of Gram-positive bacteriocins is that they are restricted to killing other Gram-positives (Riley and Wertz 2002a). The range of killing can vary significantly, from relatively narrow as in the case of lactococcins A, B, and M, which have been found to kill only *Lactococcus*, to extraordinarily broad (Martínez-Cuesta et al. 2006). For instance, some type A lantibiotics, such as nisin A and mutacin B-Ny266, have been shown to kill a wide range of organisms including *Actinomyces*, *Bacillus*, *Clostridium*, *Corynebacterium*,

Enterococcus, *Gardnerella*, *Lactococcus*, *Listeria*, *Micrococcus*, *Mycobacterium*, *Propionibacterium*, *Streptococcus*, and *Staphylococcus* (Mota-Meira et al. 2000, 2005). Contrary to conventional wisdom, these particular bacteriocins are also active against a number of medically important Gram-negative bacteria including *Campylobacter*, *Haemophilus*, *Helicobacter*, and *Neisseria* (Morency et al. 2001).

Production of bacteriocins in Gram-positive bacteria is generally associated with the shift from log phase to stationary phase. For example, nisin production begins during mid-log phase and increases to a maximum as the cells enter stationary phase (Breukink and de Kruijff 1999). The regulation of expression is not cell cycle dependent, per se, but rather culture density dependent (Dufour et al. 2007). It has been demonstrated that nisin A acts as a protein pheromone in regulating its own expression, which is controlled by a two-component signal transduction system typical of many quorum-sensing systems (Hechard and Sahl 2002). The genes involved are *nisR* (the response regulator) and *nisK* (the sensor kinase). Nisin transcription is induced by the addition of nisin to the culture medium, with the level of induction directly related to the level of nisin added (Kuipers et al. 1995).

The ecology of bacteriocins

Without question, bacteriocins serve some function in microbial communities. This statement follows from the detection of bacteriocin production in all surveyed lineages of prokaryotes (Klaenhammer 1988). What remains in question is what, precisely, that role is. Bacteriocins may serve as anti-competitors enabling the invasion of a strain into an established microbial community (Lenski and Riley 2002; Riley and Gordon 1999). They may also play a defensive role and act to inhibit the invasion of other strains or species into an occupied niche or limit the advance of neighboring cells (Riley and Wertz 2002b). *In vivo* studies had, indeed, demonstrated that bacteriocin production improves the establishment success of the producing strains (McCormick et al. 1989): *E. coli* F-18 Col⁻, a derivative of *E. coli* F-18 that no longer produces microcin V, colonize the large intestine of streptomycin-treated mice and its corresponding wild type when fed alone. Yet, when the two strains were fed together, the microcin-deficient strain was eliminated from the large intestine. Additional roles have recently been proposed for Gram-positive bacteriocins, in which they may mediate quorum sensing (Gobbetti et al. 2007) and act as communication signals in bacterial consortia, e.g., biofilms (Gillor 2007). It is likely that whatever roles bacteriocins play, these roles change as components of the environment, both biotic and abiotic, change.

Early experimental studies on the ecological role of bacteriocins were inconclusive and often contradictory (Ikari et al. 1969). More recently, a theoretical and empirical base has been established that has defined the conditions that favor maintenance of toxin-producing bacteria in both population and community settings. Almost exclusively, these studies have modeled the action of colicins. Chao and Levin (1981) showed that the conditions for invasion of a colicin-producer strain were much broader in a spatially structured environment than in an unstructured one. In an unstructured environment with mass action, a small population of producers cannot invade an established population of sensitive cells (Durrett and Levin 1997). This failure occurs because the producers pay a price for toxin production, the energetic costs of plasmid carriage, and lethality of production, while the benefits, the resources made available by killing sensitive organisms, are distributed at random. Moreover, when producers are rare, the reduction in growth rate experienced by the sensitive strain (owing to extra deaths) is smaller than the reduction felt by the producer (owing to its costs), and the producer population therefore goes extinct (Nakamaru and Iwasa 2000). In a physically structured environment, such as on the surface of an agar plate, the strains grow as separate colonies. Toxin diffuses out from a colony of producers, thus killing sensitive neighbors (Kerr et al. 2002). The resources made available accrue disproportionately to the producing colony owing to its proximity, and therefore, killers can increase in frequency even when initially rare.

Several modeling efforts have incorporated additional biological reality. Two such efforts introduced a third species, one that is resistant to the toxin but cannot itself produce the toxin (Nakamaru and Iwasa 2000). Resistance can be conferred through mutations in either the binding site or the translocation machinery required for a bacteriocin to enter the target cell. Acquisition of an immunity gene will also confer resistance to its cognate bacteriocin. It is assumed that there is a cost to resistance and that this cost is less than the cost of toxin production borne by the killer strain (Riley and Wertz 2002b). Owing to this third member, pair-wise interactions among the strains have the non-transitive structure of the childhood game of rock–scissors–paper (Karolyi et al. 2005; Kerr et al. 2002). The producer strain beats the sensitive strain, owing to the toxin's effects on the latter. The sensitive strain beats the resistant strain because only the latter suffers the cost of resistance. And the resistant strain wins against the producer because the latter bears the higher cost of toxin production and release while the former pays only the cost of resistance. In an unstructured environment, this game allows periodic cycles, in which all three types coexist indefinitely but each with fluctuating abundance (Table 1). In a structured environment, this game

Table 1 The rock, paper, scissors model of non-transitive microbial interactions

Strain below	Wins against	Loses against
Killer	Sensitive	Resistant
Sensitive	Resistant	Killer
Resistant	Killer	Sensitive

permits a quasi-stable global equilibrium, one in which all three strains can persist with nearly constant global abundance (Laird and Schamp 2008; Neumann and Schuster 2007a, b).

More recently, experimental tests of several of these theoretical conclusions have been reported. The first employed *in vitro* methods (liquid culture, static plate, and mixed plate environments) to assess the impact of local interactions and dispersal on the abundance of three strains of *E. coli* (colicin producer, colicin sensitive, and colicin resistant; Kerr et al. 2002). This study revealed that in environments where interactions and dispersal are not solely local, the resistant strain overtook the community during the course of the experiment. In contrast, in the static plate environment, where interactions and dispersal are solely local, the three phenotypes were maintained at similar densities throughout the experiment. The third environment, mixed plate, revealed that growth on a surface is not the key factor, as resistance overtook the other strains on this plate also. The critical component is whether the interactions are local or not.

The second study employed a mouse model to investigate precisely the same colicin dynamics in an *in vivo* setting, the mouse gut (Kirkup and Riley 2004). The same three strains in these experiments revealed exactly the same non-transitive interactions described above. When a mouse harbored a sensitive strain, an introduced colicin-producing strain was able to invade. When a colicin-producing strain was resident, an introduced R strain was able to invade. In both experimental systems, the non-transitive nature of colicin-mediated dynamics was further revealed (Kirkup and Riley 2004).

Numerous surveys of colicin production in natural populations suggest that populations of *E. coli* may closely match predictions of these ecological models (Riley and Gordon 1999). In *E. coli*, producer strains are found in frequencies ranging from 10% to 50% (Barnes et al. 2007; Gordon and O'Brien 2006; Gordon and Riley 1999; Riley and Gordon 1992). Resistant strains are even more abundant and are found at frequencies from 50% to 98%. In fact, most strains are resistant to all co-segregating colicins. Finally, there is a small population of sensitive cells. The models predict this distribution of phenotypes results from frequent horizontal transfer of resistance and the significant cost associated with colicin production

(Barnes et al. 2007). In other words, if a strain can gain resistance and lose production, they will over time—just as was observed in *E. coli* isolated from field mouse population over a period of 3 months (Gordon et al. 1998).

The probiotic application of bacteriocins

The GI tract

The human GI tract is a complex ecosystem in which a delicate balance exists between the intestinal microflora and the host. The microflora serves as a primary stimulus for the development of the mucosal immune system (Deplancke and Gaskins 2002; Macfarlane and Cummings 2002). Two main genera of lactic acid bacteria dominate the intestinal flora, including 56 species of *Lactobacillus* and numerous species of *Bifidobacterium*. Most of these species have been shown to produce bacteriocins *in vitro* (Avonts and De Vuyst 2001; Carr et al. 2002; Cross 2002). More recently, some of these strains have also been shown to produce bacteriocins *in vivo* (Table 2). One particularly compelling study demonstrated the *in vivo* activity of *Lactobacillus salivarius* strain UCC118, which produces a potent broad-spectrum bacteriocin (Abp118) active against the food-borne pathogen *Listeria monocytogenes* (Claesson et al. 2006). In mice, the *L. salivarius* strain provided protection against *L. monocytogenes* infection, while a mutant strain of the same species, impaired in its bacteriocin production ability, did not. Even more compelling, the bacteriocin-producing strain provided no protection against pathogen infection when mice were infected with a strain of *L. monocytogenes* expressing the cognate Abp118 immunity protein (Corr et al. 2007).

A strain of *Lactobacillus casei* L26 LAFTI was shown to significantly inhibit an enterohemorrhagic strain of *E. coli* and a strain of *L. monocytogenes* in mice (Su et al. 2007a, b), probably due to bacteriocin production (Pidcock et al. 2002). The release of bacteriocins inhibiting *Helicobacter pylori*, a human pathogen that causes severe gastroduodenal diseases (Kandulski et al. 2008), has been chiefly studied in lactobacilli strains. A BLIS with anti-*H. pylori* activity was identified in probiotic *Lactobacillus johnsonii* strain LA1 (Gotteland et al. 2008; Michetti et al. 1999) and *Lactobacillus acidophilus* strain LB (Coconnier et al. 1998). In both cases, the inhibitory activity was retained when *H. pylori* was bound to intestinal epithelial cells. Oral administration of *L. acidophilus* LB in mice protected the animals from infection with *Helicobacter felis* (Coconnier et al. 1998; Nedrud and Blanchard 2001). This PB was further shown to inhibit gastric colonization and prevent the development of gastric inflammation (Coconnier et al. 1998). Administration of *L. johnsonii* LA1 supernatant to

Table 2 Bacteriocins produced by probiotic bacteria

Bacteriocin	Producing strain	Inhibited strain(s)	Probiotic use	Reference
Gram-positive class I bacteriocins				
ABP-118	<i>Lactobacillus salivarius</i> UCC118	<i>Listeria monocytogenes</i>	Preventing gastric infection (mouse model)	Corr et al. (2007)
Bovamine™	<i>Lactobacillus acidophilus</i> <i>Propionibacterium freudenreichii</i>	<i>E. coli</i> O157:H7	Preventing colon infections in cattle	Brashears et al. (2003a); Brashears et al. (2003b)
Lacticin B	<i>L. acidophilus</i>	<i>V. anguillarum</i>	Containing Japanese flounder infections	Taoka et al. (2006)
Bacillocin 22	<i>B. subtilis</i>			
Butyricin 7423	<i>Clostridium butyricum</i>			
Salivaricin	<i>S. salivarius</i> K12	<i>S. pyogenes</i>	Treating human throat infection	Dierksen et al. (2000); Walls et al. (2003)
Salivaricin A & B		<i>S. sobrinus</i> , <i>S. mutans</i>	Preventing dental caries in human	Burton et al. (2006b); Dierksen et al. (2007)
Salivaricin B		<i>Micrococcus luteus</i> ; <i>S. anginosus</i> ; <i>Eubacterium saburreum</i>	Treating human halitosis (oral malodor)	Burton et al. (2006a)
Salivaricin	<i>S. salivarius</i> CRL1328	<i>Enterococcus</i> spp., <i>Neisseria gonorrhoeae</i>	Treating human vaginal infections	Juarez Tomas et al. (2002); Ocana et al. (1999)
UNa	<i>L. casei</i> L26	<i>E. coli</i> O111, <i>Listeria monocytogenes</i>	Containing gastric infection (mouse model)	Su et al. (2007b)
Carnocin	<i>Carnobacterium maltaromaticum</i> B26 and B33	<i>Aeromonas salmonicida</i> , <i>Y. ruckeri</i>	Containing Rainbow trout infections	Kim and Austin (2006)
UN	<i>L. johnsonii</i> La1	<i>H. pylori</i>	Preventing human gastric infections	Cruchet et al. (2003); Gotteland and Cruchet (2003)
UN	<i>L. acidophilus</i> LB	<i>H. pylori</i> , <i>H. felis</i>	Containing human gastric infections	Coconnier et al. (1998); Michetti et al. (1999)
Gram-positive class II bacteriocins				
Pediocin	<i>Pediococcus acidilactici</i>	<i>Enterococcus</i> , <i>L. monocytogenes</i> , <i>Klebsiella</i> , <i>Pseudomonas</i> , <i>Shigella</i>	Containing human gastric infections	Speelmans et al. (2006)
Enterocin	<i>Enterococcus faecium</i> EK13	<i>Salmonella dusseldorf</i> SA13	Reducing Japanese quails (poultry) infections	Laukova et al. (2003)
		<i>E. coli</i> , <i>Clostridia</i> sp.	Preventing rabbit gastric infection	Laukova et al. (2006)
		<i>Salmonella pullorum</i>	Containing young broiler chickens GI infections	Audisio et al. (2000)
Gram-negative bacteriocins				
UN	<i>A. media</i> A199	<i>V. tubiashii</i> , <i>Saprolegnia parasitica</i>	Containing Pacific oyster larvae and eel infections	Gibson et al. (1998); Lategan et al. (2004)
UN	<i>A. hydrophila</i> <i>V. fluvialis</i>	<i>A. salmonicida</i>	Containing Rainbow trout infections	Irianto et al. (2003)
UN	<i>Roseobacter</i> sp. BS107	<i>Vibrio</i> spp.	Containing Scallop larvae infections	Ruiz-Ponte et al. (1999)
Colicins				
Colicin E2, E8 and E7	<i>E. coli</i>	<i>E. coli</i> O157:H7	Inhibiting calves GI contamination	Murinda et al. (1996)
Colicin E7	<i>E. coli</i>	<i>E. coli</i> O157:H7	Reducing calves and adult cattle GI contamination	Schamberger et al. (2004)
Colicin E1 and Ib	<i>E. coli</i> H22	<i>E. coli</i> and <i>Enterobacter</i> spp.	Inhibiting GI enteric infection (mouse model)	Cursino et al. (2006)
Microcins				
Microcin 24	<i>E. coli</i>	<i>S. typhimurium</i>	Inhibiting adult chickens GI infection	Portrait et al. (1999); Wooley et al. (1999)

Table 2 (continued)

Bacteriocin	Producing strain	Inhibited strain(s)	Probiotic use	Reference
Microcin B17	<i>E. coli</i> Nissle 1917	<i>E. coli</i>	Reducing calves (cattle) colon infection	von Buenau et al. (2005)
		<i>S. typhimurium</i> , <i>Shigella flexneri</i> , <i>E. coli</i>	Treating acute infant and toddlers diarrhea	Henker et al. (2007)
Microcin C7	<i>E. coli</i> H22	<i>Shigella flexneri</i>	Inhibiting GI enteric infection (mouse model)	Cursino et al. (2006)

^a Unnamed bacteriocin

adult patients colonized by *H. pylori* significantly decreased infection (Gotteland et al. 2008; Gotteland and Cruchet 2003), while oral consumption of the live bacteria by school children, which were found to be *H. pylori* positive, resulted in a significant decrease in urease production (Cruchet et al. 2003). Mutacin B-Ny266, a lantibiotic produced by *Streptococcus mutans*, was recently shown to inhibit a broad spectrum of multi-resistant pathogens including staphylococci, streptococci, and *Neisseria* strains (Mota-Meira et al. 1997, 2000; Parrot et al. 1990) and was found active against methicillin-resistant *Staphylococcus aureus* when assayed in a mouse model (Mota-Meira et al. 2005)

Most of the members of class IIa bacteriocins have relatively narrow killing spectra compared to those in class I and inhibit only closely related Gram-positive bacteria (Heng et al. 2007). However, there are exceptions, such as pediocin, which has a fairly broad inhibitory spectrum and can inhibit *Streptococcus aureus* and vegetative cells of *Clostridium* spp. and *Bacillus* spp. and *Listeria* (Cintas et al. 1997; Eijsink et al. 2002; Nes and Holo 2000; van Reenen et al. 1998). A pediocin-producing strain of *Pediococcus acidilactici*, able to survive in the GI tract, was recently isolated and found to be an effective inhibitor of several Gram-positive bacterial pathogens, such as *Enterococcus* spp. (including vancomycin-resistant strains) and *L. monocytogenes*. Furthermore, it inhibited gastric adhesion of opportunistic pathogens from *Klebsiella*, *Pseudomonas*, and *Shigella* genera (Piva and Casadei 2006; Speelmans et al. 2006). Another promising probiont is the bacteriocin producer *Enterococcus mundtii* strain ST4SA, active against a number of Gram-positive bacteria, including *Enterococcus faecalis*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*, as well as the Gram-negative bacteria *P. aeruginosa* and *K. pneumoniae* (Granger et al. 2008). The survival, persistence, and bacteriocin production of this strain were successfully evaluated within the GI tract of pigs.

One weakness of the bacteriocins produced by Gram-positive bacteria, with respect to their use in probiotic applications, is that they seldom inhibit commonly encountered enteropathogenic bacteria such as *Enterobacter*, *Klebsiella*, or *Salmonella*. However, bacteriocins produced

by Gram-negative bacteria can accomplish this task (see Table 2). For example, *E. coli* strain H22 inhibited the growth of seven genera of the family *Enterobacteriaceae* (*Enterobacter*, *Escherichia*, *Klebsiella*, *Morganella*, *Salmonella*, *Shigella*, and *Yersinia*). The observed inhibition was attributed to the production of microcin C7 (Smajs et al. 2008) and colicins E1 and Ib, as well as aerobin and an unidentified phage (Cursino et al. 2006). Simultaneous administration of the probiont and the enteric pathogen *Shigella flexneri* to germ-free mice resulted in a strong inhibition of the pathogen, which was attributed to its microcin production (Cursino et al. 2006). A more widely used enteric probiont is *E. coli* strain Nissle 1917, originally isolated from the feces of a soldier who did not develop diarrhea during a severe outbreak of shigellosis (Snelling 2005). Some of the beneficial properties of this strain may be attributable to bacteriocin production, as this strain was shown to produce two microcins, H47 and M (Patzer et al. 2003). However, Altenhoefer et al. (2004) claimed that a microcin-negative mutant was as effective as the parent strain in protecting gnotobiotic piglets from *Salmonella* infection.

The oral cavity and respiratory tract

Streptococci, in particular, *S. mutans* and *Streptococcus salivarius*, are considered the principal etiological agents of dental caries in humans (Hillman et al. 2007; Quivey et al. 2000). *S. mutans* produces mutacins active against neighboring plaque-forming strains, and a positive correlation exists between bacteriocin production and the ability to colonize the oral cavity. A nonpathogenic mutacin-producing strain was constructed for use in dental caries replacement therapy (Hillman 2002; Hillman et al. 2007), one that lacked one of the primary pathogenic traits of *S. mutans*, lactate dehydrogenase production. This strain was able to colonize the mouth in an animal model, was stably maintained for up to 6 months, and was less pathogenic to the host (Hillman 2002; Hillman et al. 2000). Human trials revealed that the strain was retained for 14 years following a single application and appeared to competitively exclude colonization by other *S. mutans* strains (Hillman et al. 1987, 1985; Hillman and Socransky 1987; Smith et al. 2007).

S. salivarius K12 produces two potent lantibiotics, salivaricin types A and B. This strain is employed to treat infections of the upper respiratory tract caused by streptococcal organisms, including treatment of dental caries caused by *S. sobrinus* and *S. mutans* (Balakrishnan et al. 2000). Salivaricin B was successfully used to treat halitosis caused by *Prevotella* spp., *Eubacterium saburreum*, and *Micromonas micros* (Burton et al. 2006a, 2005). A newly developed lozenge and chewing gum, which incorporate the salivaricin-producing strain is marketed by BLIS® technologies (<http://www.blis.co.nz>), which claims it safely improves halitosis by restoring the “normal” oral cavity microflora (Burton et al. 2006b; Tagg et al. 2006).

Streptococcus pyogenes is a common human commensal, with 5–15% of the human population harboring the bacterium, usually in the respiratory tract, without signs of disease. However, strains of *S. pyogenes* can become pathogenic when host defenses are compromised (Cappelletty 1998). For example, when *S. pyogenes* is introduced or transmitted to vulnerable tissues, a variety of infections can occur, including pharyngitis (strep throat), scarlet fever, and skin infections (Cunningham 2000). The ability of the normal flora of the upper airways to inhibit growth of potential pathogens *in vitro* has been well documented (Brook 2005; Nizet 2007). *S. salivarius*, isolated from the nasopharynx of children who rarely suffered from throat infections, were found to produce bacteriocins with anti-*S. pyogenes* activity. In the lab, this bacteriocin was able to kill a range of other human pathogens, including *Moraxella catarrhalis* and *Haemophilus influenza* (Walls et al. 2003). Children consuming milk supplemented with a salivaricin-A-producing strain, *S. salivarius* 20P5, showed markedly increased salivaricin A inhibitory activity on their tongue, which may provide protection against *S. pyogenes* infection (Dierksen et al. 2007).

In the oral cavity, the presence of salivaricin-producing *S. salivarius* has been shown to reduce the frequency of acquisition of *S. pyogenes* in schoolchildren (Brook 2005). A strain of *S. salivarius* K12-producing salivaricins A and B was isolated for use as a dietary supplement (Tagg and Dierksen 2003). This strain has been incorporated into a throat guard spray that aims to “assist in maintaining a healthy throat” and was shown to reduce throat infections in children (<http://www.blis.co.nz>). Four lozenges containing a bacteriocin-producing strain of *S. salivarius* were administered per day over 3 days, and the strain was shown to persist and produce the toxin in different sites of the oral cavity for as long as 3 weeks (Horz et al. 2007).

The vagina

The healthy human vaginal microbiota is dominated by *Lactobacillus crispatus*, *Lactobacillus jensenii*, *Lactobacillus*

iners, and *Lactobacillus gasseri* (Vasquez et al. 2002). In contrast, the vaginal microbiota of women with bacterial vaginosis is dominated by *Gardnerella vaginalis*, *Mycoplasma hominis*, *Prevotella*, *Peptostreptococcus*, *Mobiluncus* spp., and *Bacteroides* spp., while lactobacilli are found at lower densities (Falagas et al. 2007; O’Brien 2005). Bacteriocin production by probiotic lactobacilli strains was found to inhibit the growth of some of these infectious pathogens: *L. acidophilus* and *L. jensenii* strain 5L08 showed antagonistic activity against *G. vaginalis*. BLIS produced by *Lactobacillus pentosus* and *L. jensenii* 5L08 inhibit the growth of *Candida albicans* (Aroutcheva et al. 2001; Kaewsrichan et al. 2006). *L. pentosus* strain NCIMB 41114 was patented for its use as a probiotic agent because it competitively excludes various species of *Candida* (Wynne et al. 2006).

The most promising vaginal probiont to date is a vaginal isolate of *L. salivarius* strain CRL 1328, found to release a BLIS able to inhibit the growth of certain strains of *Enterococcus* spp., as well as *Neisseria gonorrhoeae* (Ocana et al. 1999). This strain was evaluated for the impact of pH, temperature, and culture medium on bacteriocin production (Juarez Tomas et al. 2002), as well as viability after long-term storage using freeze drying and capsulation (Juarez Tomas et al. 2004), all of which were found to have no apparent effect on the bacteriocin activity. This strain is able to bind successfully to epithelial cells, an important step in probiotic colonization (Ocana and Nader-Macias 2001) while significantly reducing the adherence of the urogenital pathogen *Staphylococcus aureus* (Zarate and Nader-Macias 2006).

Livestock

It is often important to control the overgrowth of potentially pathogenic bacteria in animal feedstock, particularly those that might be infectious to downstream consumers (Braden 2006; Hussein 2007). For example, newly hatched broiler chickens are not exposed to maternal feces and thus receive neither the maternal bacterial flora nor the normal induction of their immune system. Consequently, supplying probiotic supplements to these chicks is critical for safe poultry husbandry (Pascual et al. 1999; Revollo et al. 2006). Administration of the bacteriocin-producing *Enterococcus faecium* strain J96 shortly after hatching increased the survival rate of young broiler chicks challenged with the poultry pathogen *Salmonella pullorum* (Audisio et al. 2000). Interestingly, the probiont was not efficient as therapeutic treatment following infection.

Some *Salmonella* spp. may colonize the GI tracts of chickens without any deleterious effects on the birds; yet, upon consumption, humans may experience severe intestinal diseases (Revolledo et al. 2006). A promising antago-

nistic to *Salmonella dusseldorf* strain SA13 is the PB *E. faecium* strain EK13, which produces enterocin A, tested in gnotobiotic Japanese quails, and its presence resulted in a reduction in pathogen concentrations (Laukova et al. 2006). Microcins produced by *E. coli* hold promise in reducing the abundance of *Salmonella typhimurium* in adult chickens (Gillor et al. 2004; Portrait et al. 1999). Wooley and colleagues (Wooley and Shotts 2000) transformed plasmids containing microcin 24 gene fragments into a nonpathogenic avian *E. coli* strain. The addition of the recombinant probiont to the drinking water of chickens significantly reduced the abundance of *S. typhimurium* (Wooley and Shotts 2000).

In cattle, the cow's rumen serves as a major reservoir for *E. coli* O157:H7, a pathogen that is exceedingly difficult to control using antibiotics (Hussein 2007; Hussein and Bollinger 2005). In fact, studies have shown that antibiotic treatment increases the amount of shiga toxin released by this pathogen, resulting in higher levels of bacterial virulence. Recently, there have been reports that administration of colicin-producing bacteria into the rumen of cows can reduce the level of enteric pathogens in the animal (Diez-Gonzalez 2007). For example, *E. coli* O157:H7 cells could not be detected in most calves treated with colicin-producing *E. coli* strains (Schamberger et al. 2004). Seven colicin-producing strains were isolated from infected adult cattle and yielded efficacious results against enterohemorrhagic *E. coli* (Schamberger and Diez-Gonzalez 2004). Colicin E7 was shown to inhibit the colonization of infectious strains in the cow's rumen (Schamberger et al. 2004). A mixture of colicin E7-producing strains was shown to reduce the level of colonization of the virulent *E. coli* strains in treated calves. The microcin B17-producing *E. coli* strain Nissle 1917 was able to reduce by half the incidence of calf diarrhea (von Buenau et al. 2005). A mixture of *L. acidophilus* and *Propionibacterium freudenreichii* also reduced levels of *E. coli* O157:H7 colonization in cattle, and it is currently being marketed as a probiotic under the trade name of Bovamine™ (<http://www.bovamine.com/>).

There is a growing interest in producing rabbit meat, as it requires less land, the animals are highly fertile, and the meat provides a good protein source low in fat and cholesterol (Flachowsky 2002). However, young rabbits are susceptible to infectious agents such as *E. coli* and *Clostridia* (Rodriguez-Calleja et al. 2004). LAB are rarely found in rabbits but enterococci are prevalent in their GI tract (Linaje et al. 2004). *E. faecium* EK13 is an enterocin-A-producing strain with probiotic properties that was found to persistently colonize the rabbit GI tract with an apparent effect on its microflora, reducing colonization of pathogenic *Staphylococcus* spp. (Laukova et al. 2006).

The bacteriocin-producing strain *L. salivarius* DPC6005 was fed to pigs together with four other *Lactobacillus*

strains (Walsh et al. 2008) and was found to be the predominant strain detected both in the ileum digesta and bound to the ileal mucosa. *L. salivarius* DPC6005 produces an antilisterial bacteriocin, salivaricin P, which is also highly active against lactic acid bacteria, including lactobacilli and *Enterococcus* spp. (Barrett et al. 2007). Bacteriocin production may have permitted the strain to outcompete the resident gut microbial communities and colonize the ileum better than the other four co-administered strains (Walsh et al. 2008).

Aquaculture

Aquatic cultures are continuously exposed to a wide range of microorganisms, some of which are pathogenic (Reilly and Kaferstein 1999). Efforts to prevent and control invasion by disease-causing agents have concentrated on good husbandry techniques and the use of vaccines (Corripio-Miyar et al. 2007) and antibiotics (Smith 2007). These methods can result in an improvement in the organism's immunity by reducing stress but cannot prevent disease outbreak. The use of vaccines is laborious, costly, and highly stressful to the animals. The use of antibiotics will result in the selection for antibiotic-resistant bacteria and the residues of the drugs remain active long after use, either as free unused antibiotic or extracted from the water by the cultured animals (Alderman and Hastings 1998; Matyar 2007; Prater 2005).

An alternative approach to disease prevention in aquaculture is the use of bacteriocin-producing PB (Laukova et al. 2003). Administration of PB was reported to competitively exclude pathogenic bacteria through the production of inhibitory compounds, improve water quality, enhance the immune response of host species, and enhance the nutrition of host species through the production of supplemental digestive enzymes (Thompson et al. 1999; Verschuere et al. 2000). PB has the potential to serve as an efficacious long-term solution, as the administered bacteria become established in the host and/or the aquatic environment. Early attempts to use probiotic species in aquaculture usually employed PB developed for terrestrial animals, which contained the facultative or obligate Gram-positive anaerobes found in the GI tract, specifically of the genera *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* (Gatesoupe 1999; Gatesoupe 2008). Production of PB specifically for the use in aquaculture is now a more popular approach, as these strains are more likely to establish in aquatic communities (Irianto and Austin 2002a).

The Gram-negative facultative anaerobes *Vibrio* and *Pseudomonas* are often found in crustaceans, bivalves, and marine fish, while the freshwater environment is dominated by *Aeromonas*, *Plesiomonas*, and *Enterobacteriaceae* (Irianto and Austin 2002a). Nutrient and water enrichment with commercial PB, designated Alchem Poseidon™ (a

mixture of *Bacillus subtilis*, *L. acidophilus*, *Clostridium butyricum*, and *Saccharomyces cerevisiae*), administered to Japanese flounder significantly enhanced lysozyme activity, lowered levels of mucosal proteins and also improved survival after bacterial immersion challenge with *Vibrio anguillarum* (Taoka et al. 2006). Previously, these bacterial species were shown to produce potent bacteriocins: bacillocin 22 and a BLIS were identified in *B. subtilis* cultures (Zheng and Slavik 1999), lactacin and acidocin in *L. acidophilus* (Dobson et al. 2007; Han et al. 2007), and butyricin 7423 in *C. butyricum* (Clarke and Morris 1976). It is likely thus that these toxins play a role in controlling opportunistic aquaculture pathogens.

Aeromonas media strain A199 was found to produce several BLIS and was shown to control infection by *Vibrio tubiashii* in pacific oyster larvae (Gibson et al. 1998) and reduce saprolegniosis-related mortality in eels (Lategan et al. 2004). Irianto and Austin (2002b) reported that cultures of *Aeromonas hydrophila* and *Vibrio fluvialis* were effective at controlling infections by *Aeromonas salmonicida* in rainbow trout. In addition, Ruiz-Ponte found that BLIS-producing *Roseobacter* sp. strain BS107 inhibits the pathogenic affect of *Vibrio* spp. resulting in enhanced survival of scallop larvae (Ruiz-Ponte et al. 1999).

Conclusion

There has been a virtual explosion of research in the broad field of probiotics. One particularly compelling area of study involves the use of both *in vitro* and *in vivo* studies aimed at determining the impact of bacteriocin production on a strain's ability to provide a positive health benefit to the host. This review has highlighted the most promising of these studies, including those involving human, animal, and aquaculture applications. The striking successes of these studies, coupled with the extensive literature on the evolution and ecology of bacteriocins, has resulted in the identification of a promising alternative to classical antibiotic use.

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