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Alternative solutions to antibiotics in *mastitis* treatment for dairy cows - a review*

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Mastitis is one of the most common diseases in dairy cows and it is responsible for the greatest economic losses on dairy farms. It is caused by many different strains of bacteria, fungi and algae. Treatment of mastitis mainly relies on antibiotics. However, the long-term use of antibiotics in dairy cows has led to increased drug resistance of the pathogens causing *mastitis*. Therefore, alternative methods for the elimination of pathogenic microorganisms causing *mastitis* are being investigated. Such methods include the use of nanotechnology, bacteriophage therapy, plant extracts, proteins of animal origin and bacteriocins. The main advantage of these solutions is that pathogens do not become resistant to the substances used. Thus, they may in the future become the main forms of mastitis therapy. *In vitro* and *in vivo* studies of alternative treatments for *mastitis* have revealed successful inhibition of growth and destruction of many pathogens responsible for this disease. This article presents a review of alternative solutions that may become popular in mastitis treatment in dairy cattle herds.

KEY WORDS: *mastitis* / nanoparticles / bacteriophages / plants / animal protein / bacteriocins

Mastitis is one of the most common diseases in dairy cows, causing large economic losses for breeders due to decreased milk production and deterioration of its chemical

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parameters [Seegers et al. 2003, Halasa et al. 2007]. Pathogens most frequently causing mastitis include bacteria, e.g. *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus uberis*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae, Escherichia coli, Enterococcus* spp. and *Pseudomonas spp.,* fungi such as *Candida* spp. or *Cryptococcus* spp., and algae, e.g. *Prototheca* [Kalińska *et al.* 2018]. It is estimated that in Poland the clinical form of mastitis affects 6.5% of udder quarters, while the sub-clinical form was observed in 43.4% of the cases studied [Smulski *et al.* 2011]. Problems with mastitis in dairy cattle are found worldwide. The incidence of mastitis, pathogens, prevention and treatment methods, as well as effectiveness of applied therapy have been investigated in numerous studies in various countries worldwide [Wolf *et al.* 2012, Petrovski *et al.* 2015, Cheng *et al.* 2019].

Mastitis in dairy herds leads to increased somatic cell counts (SCC), which causes losses to both producers and milk processors [Jóźwik *et al*. 2010, 2012ab]. Increased SCC results in a reduction of milk yield of cows [Strzałkowska *et al*. 2009ab, Bagnicka *et al.* 2010, 2011, Jóźwik *et al*. 2010] as well as cheese yield from milk obtained from affected animals. In addition, mastitis is one of the main reasons for culling cows in herds. It has been estimated that on Polish farms between 5.38% and 16.13% of cows are culled due to mastitis [Neja *et al.* 2015, Kalińska and Slósarz 2016].

Treatment and prevention of mastitis mainly rely on antibiotics, but their efficacy is decreasing because of growing drug resistance in bacteria [Unakal and Kaliwal 2010]. This problem has been attributed to the overuse of antibiotics in treatment of animals, contributing to the emergence of strains resistant to therapies [Olivier and Murinda 2012]. Many authors have emphasized the increasing resistance of major mastitis pathogens to antibiotics [Gao *et al.* 2012, Wang *et al.* 2015, Gao *et al.* 2019].

Currently, many studies focus on investigating alternative methods of animal treatment which would reduce the amount of antibiotics used in the prevention and treatment of animal diseases, thus limiting pathogen resistance to the drugs used [Hendriksen *et al.* 2008, Kalińska *et al.* 2019].

The aim of this paper is to present the current state of knowledge concerning alternative solutions in mastitis treatment and prevention in dairy cows.

Nanotechnology in mastitis treatment

Nanotechnology is one of the most rapidly developing scientific disciplines and properties of nanoparticles are increasingly used in the veterinary, pharmaceutical and human medicine industries. The unique chemical and physical properties, as well as a large surface area in relation to their volume, make nanomaterials an alternative in controlling pathogens, including those that cause mastitis in dairy cows [Kim *et al.* 2007]. According to literature data, silver, gold and copper nanoparticles are the most commonly used in the elimination of pathogenic microorganisms [Zhang *et al.* 2008, Raffi *et al.* 2010, Wernicki *et al.* 2014].

Bactericidal and fungicidal properties of silver nanoparticles are connected with rupture of cell membranes by denaturing proteins, creating a microenvironment saturated with silver ions, inhibiting DNA replication, forming reactive oxygen species and expressing proteins and enzymes involved in the respiratory chain [Li *et al.* 2010]. The toxic effect of copper nanoparticles on pathogens is based on the production of reactive oxygen species, the destruction of the DNA chain, and lipid and protein peroxidation [Li *et al.* 2012]. In turn, gold nanoparticles change the membrane potential and activity of adenosine triphosphate synthesis in a pathogen cell, which leads to the inhibition of metabolism in pathogenic bacterial strains [Shamaila *et al.* 2016]. The effectiveness of therapy with nanoparticles depends mainly on the cell wall structure in the pathogenic microorganism. Copper nanoparticles show greater toxicity to Gram-positive bacteria with thicker cell walls, whereas Gram-negative bacteria are more sensitive to silver and gold nanoparticles [Azam *et al.* 2012, Radzig *et al.* 2013].

Studies by Dehkordi *et al.* [2011] demonstrated that a 10 µg/ml solution of silver nanoparticles successfully destroyed *S. aureus* isolated from cows with mastitis after about seven minutes of incubation. Kim *et al.* [2007] reported that silver nanoparticles in low concentrations kill *E. coli* strains, but have a much less toxic effect on *S. aureus*. The antimicrobial activity of silver nanoparticles on Gram-negative bacteria was demonstrated by Sondi and Salopek-Sondi [2004]. It has been found that nanosilver is an effective bactericidal agent. Electron microscopy of *E. coli* cells showed cell damage, impairment of normal transport across the plasmatic membrane, and finally cell death. Jain *et al.* [2009] investigated a gel formulation containing nanosilver and found it was effective against *E. coli*, *S. typhi*, *S. epidermidis* and *S. aureus*, *Pseudomonas aeruginosa,* as well as *Candida* yeast-like fungi. The lowest minimum inhibitory concentration (MIC) causing the death of 50% of strains was found for *E. coli* (1.56 µg/ml), while it was highest for *S. aureus* (6.25 µg/ml). Previous papers revealed that *E. coli* and *P. aeruginosa* are the most vulnerable to silver nanoparticles and *S. aureus* bacteria are the least vulnerable. In a study on *Pseudomonas aeruginosa* and *S. aureus* strains isolated from milk of mastitis-infected goats, Yuan *et al.* [2017] found that the MIC for silver nanoparticles was 1 and 2 µg/ml, respectively. Those authors indicated that bacterial strains treated with nanoparticles had a lower expression of glutathione, a downregulation of both superoxide dismutase and catalase, but a higher expression of glutathione S-transferase.

Studies by Ren *et al.* [2009] revealed that copper oxide nanoparticles reduced the populations of pathogenic bacterial strains, including methicillin-resistant *S. aureus* and *E. coli*, with an MBC in the range of 100 µg/ml up to 5000 µg/ml. They also showed that a combination of copper oxide and silver nanoparticles completely reduced pathogenic bacteria. In their study on properties of monodisperse copper particles Kruk *et al*. [2015] demonstrated that copper nanoparticles exerted strong activity against Gram-positive bacteria, including methicillin-resistant strains of *S. aureus,* comparable to nanosilver, but also showed a fungicidal effect against *Candida* spp. The antibacterial activity of 7-epiclusianone extracted from *Rheedia brasiliensis* fruit and its novel copper metal complex on *Streptococcus* spp. strains isolated from bovine mastitis was investigated by de Barros *et al.* [2017]. The study demonstrated that the complex had an MIC of 7.8 μg/ml and an MBC from 15.6 to 31.3 μg/ml against the isolated pathogen. The antibacterial properties of such compounds indicate their applicability in mastitis treatment.

Studies on the potential applications of gold nanoparticles in controlling pathogens causing mastitis demonstrated greater efficacy on Gram-negative bacteria, while the bactericidal effect on Gram-positive bacteria required about 50% larger nanoparticles [Umadevi *et al.* 2011]. Gold nanoparticles also showed activity against fungal pathogens causing mastitis [Wani and Ahmad, 2013]. The advantage of using nanogold comes from its lower toxicity compared to other nanoparticles [Sreekanth *et al.* 2012]. Shamaila *et al.* [2016] reported MICs of 7-34 nm gold nanoparticles to be 2.93 μg/ml and 3.92 μg/ml for *E. coli* and *S. aureus,* respectively. Omara [2017] investigated the *in vitro* activity of honey and gold nanoparticles on methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA) isolated from milk of mastitis-infected cows. His study demonstrated that 30 nm gold nanoparticles had an inhibitory effect on growth of MRSA and VRSA when used at a concentration of 2.56 μg/ml, while for a mixture of nanogold with honey from citrus fruit the MIC was about 50% lower.

Researchers are currently working on developing intramammary preparations using metal nanoparticles. The promising results of *in vitro* studies are prompting a growing number of scientists to conduct further *in vivo* experiments [Rejendran 2013, Kalińska et al. 2019]. Many factors indicate that in a few years the first commercial intramammary preparations containing silver, gold or copper nanoparticles will be developed.

Bacteriophage therapy

Bacteriophages are a group of viruses that are widely distributed in nature and targeted at bacterial hosts. They are composed of genetic material (DNA or RNA) coated with structural proteins called capsids [Ackermann and DuBow 2011]. They may be isolated from fresh and saline water, sewage and soil, as well as living organisms. Once the phage has penetrated the bacterial cell, it can use the lytic life cycle to infect the host cell, leading to the total destruction of the cell and the subsequent release of new phages into the environment. After destroying the cell using lytic enzymes, bacteriophages can attack other bacterial pathogens [Maurice *et al.* 2013]. In a single lytic cycle, depending on the bacteriophage and bacterial host, 50 to 1000 new phages are released into the environment, and each phage can destroy and infect other bacterial pathogens [Ackermann and DuBow 2011]. Carlton [1999] reported that after the destruction of one bacterial cell on average 200 progeny phages are released and each of them infects and kills further cells. This leads to their lysis and the release of new phages, their number reaching more than 40,000 after the second lytic cycle and over 8 million after the third lytic cycle. According to Duckworth and Gulig [2002], on average bacteriophages can go through four lytic cycles per hour. Bacteriophages may also use the lysogenic life cycle, which is much less aggressive and does not end with the destruction of the bacterial cell. The genetic material of the phage penetrates the bacterial cell. It is built into the bacterial chromosome to form the prophage and replicates with host DNA. In bacteria exposed to stress conditions, the prophage can become active and use the lytic life cycle, which leads to cell lysis [Weber-Dąbrowska et al. 2006].

Bacteriophages are used in medicine for the treatment of infections caused by bacteria resistant to antibiotics [Górski *et al.* 2007]. A number of studies on phage therapy have been conducted on various groups of farm animals [Xie *et al.* 2005, Hosseindoust *et al.* 2017]. Studies carried out on poultry, piglets and calves infected with *E. coli* strains have demonstrated that the administration of phage cocktails inhibited food poisoning and reduced mortality in animals, with bacteriophage therapy being effective in the control of infections caused by this pathogen. There is a commercially available product containing bacteriophages against *E. coli* and eliminating from 95 to 100% of these pathogenic microorganisms [Sillankorva *et al.* 2012]. In the future, phage cocktails may be an option for the treatment and prevention of mastitis caused by *E. coli* [Tsonos *et al.* 2014]. Kropiński *et al.* [2011] showed over 50% *in vitro* efficacy of a cocktail containing four types of phages in the growth inhibition of *E. coli* strains isolated from milk of cows with mastitis. Moreover, McLean *et al.* [2013] demonstrated that *E. coli* may be reduced completely in raw milk at a temperature of 25°C.

Phage therapy may also be used for the treatment of mastitis caused by antibiotic-resistant bacteria [Gomes and Henriques 2006]. Most researchers have focused on the possibility of applying bacteriophage K (staphylococcal) therapy to treat mastitis caused by *S. aureus*. Gill *et al.* [2006] treated lactating dairy cows with mastitis caused by *S. aureus* with infusions of bacteriophage K for five days. The researchers reported that 16.7% of udder quarters were cured after phage therapy. They also claimed that the options for the use of phage therapy are limited, because bacteriophage K is destroyed by the immune system of cows and whey proteins in milk. Thus further research is needed to develop more effective ways of administering such phages. O'Flaherty *et al.* [2005] demonstrated that bacteriophage K destroys *S. aureus* strains in heated milk, whereas in raw milk the lysis of the pathogen is inhibited because the pathogenic bacteria form aggregates. Studies on the treatment of mastitis caused by *S. aureus* also revealed the potential application of a *Myoviridae* bacteriophage. Han *et al.* [2013] reported that bacteriophage SAH-1 isolated from wastewater sampled near a farm inhibited bacterial growth *in vitro*, and thus it could be used for the treatment and prevention of *S. aureus* infections. Bacteriophage SPW isolated and described by Li *et al.* [2014] exhibited strong lytic properties in a bacteriolytic activity test with cells of pathogenic *S. aureus.* Those authors also showed that pathogenic cells were destroyed in a wide range of temperatures and pH levels, as well as in the presence of chemical reagents. They also found that bacteriophage SPW is highly resistant to UV radiation (94% of the bacteriophage population survived a 40-minute exposure to UV), which is one of the primary factors reducing bacteriophage populations in the natural environment [Jończyk *et al*. 2011]. Dias *et al.* [2013] isolated *Myoviridae* bacteriophages from locally sampled wastewater and reported that under *in vitro* conditions they destroyed penicillin- and ampicillin-resistant *S. aureus*.

Phage therapy may in the future become one of the main methods for mastitis treatment in dairy cows and limit the use of antibiotics. However, further research is needed to identify the most effective ways to administer bacteriophages to animals affected by this disease.

Antibacterial activity of herbs, plants and plant extracts

Plants and plant extracts have been used for millennia. Before synthetic drugs were invented they had been the basis for treatment of many diseases in humans and animals [Huminiecki *et al*. 2017, Huminiecki and Horbańczuk 2018, Islam *et al*. 2018, Mozos *et al.* 2018, Wang *et al*. 2018, Yeung *et al*. 2018, 2019, 2020]. They are currently one of the main agents for the treatment of animals on organic farms, where the use of antibiotics is allowed only as a last resort [Ruegg 2009, Mushtaq *et al.* 2018]. Plants with bacteriostatic properties provide a potential alternative method of treating mastitis in dairy cows. The main advantage of the biological compounds contained in plants is that they do not induce resistance in bacteria, and therefore can be used over a long period. Studies have shown the effectiveness of many biologically active compounds contained in plants in the treatment of mastitis [Diaz *et al.* 2010].

Research on the alternative treatment of mastitis with plants, herbs and plant extracts has involved plants both well-known and commonly used to cure colds in humans and animals, and plants growing only in certain geographical regions [Kalayou *et al.* 2012, Laudato and Capasso 2013]. Poeloengan [2011] investigated the effect of red ginger on the growth of *S. aureus, S. epidermidis* and *S. agalactiae* isolated from milk of cows with mastitis. Experiments showed the antimicrobial effect of red ginger extract. *In vitro* studies demonstrated that all bacteria tested were sensitive to red ginger extract, but the strongest growth inhibition was found in *S. epidermidis*. Other studies revealed the antibacterial effect of caprylic acid contained in coconut oil in the treatment of mastitis. Nair *et al.* [2005] reported that caprylic acid exerted bactericidal activity against five major pathogens causing mastitis: *S. aureus, S. agalactiae, S. dysgalactiae, S. uberis* and *E. coli*., and reduced growth of all strains by >5.0 log cfu/mL after six hours of incubation. Of all the above-listed bacteria, streptococci were the most sensitive to caprylic acid. The use of alternative plant-derived compounds against the same pathogens was investigated by Baskaran *et al.* [2009]. They studied the bactericidal properties of trans-cinnamic acid (TC) aldehyde, eugenol, carvacrol and thymol, which are components of essential oils. Their experiments revealed that all plant-derived compounds had bactericidal effects on the major pathogens causing mastitis in dairy cows. TC demonstrated the strongest activity, with the tests showing complete inhibition of bacterial growth after 12 hours. The bactericidal effect of TC derived from cinnamon cassia oil was also confirmed by Zhu *et al.* [2016]. Staining tests revealed membrane damage in *S. aureus* and *E. coli* cells incubated with cinnamon oil, with the bacterial cell count dropping to an undetectable level after eight hours of the experiment. The bactericidal effect of essential oils obtained from *Thymus vulgaris* and *Lavandula angustifolia* was reported by Abboud *et al.* [2015] for *in vitro* and *in vivo* studies. Both essential oils demonstrated strong bactericidal properties against staphylococcal and streptococcal strains causing mastitis in herds of cows from four different farms. Those researchers showed that the bactericidal effects of these oils were similar to those obtained in the control cows treated with antibiotics. *In vivo* tests involving an intramuscular injection of a 10% solution of essential oils showed the complete elimination of pathogens from milk of treated cows. Essential oils have also been used in the treatment of mastitis caused by *Prototheca* algae. Grzesiak *et al.* [2018] investigated the effects of essential oils extracted from *Thymus vulgaris L., Origanum vulgare L., Origanum majerana L., Mentha × piperita L.* and *Allium ursinum L* on strains of *Prototheca zopfii* isolated from cow's milk. A combined analysis of sensitivity of algal strains to chemotherapeutics showed that they were resistant to most of the recommended drugs. Those researchers found that *Prototheca zopfii* strains were sensitive to essential oils from *Origanum majerana L., Thymus vulgaris L.,* and *Origanum vulgare L.,* with an MIC ranging from 0.25 to 1 μl/ml. The strongest activity was observed for essential oil from *Origanum majerana L*.

Aquatic plants are also potential sources of antimicrobial compounds for the treatment of mastitis. Rossi *et al.* [2011] investigated the effects of extracts from two aquatic plants, *Salvinia auriculata* and *Hydrocleys nymphoides,* combined with organic compounds (ethanol, ethyl acetate, dichloromethane) on *S. aureus* and *S. agalactiae* strains, and demonstrated the antimicrobial activity of the extracts against the tested pathogens. Their study revealed a complete reduction of pathogens in the samples after a 24-hour incubation of bacterial strains with extracts at their MICs.

Plant-derived extracts may also be used in the treatment of mastitis caused by fungal pathogens. Ksouri *et al.* [2017] reported a strong antifungal activity of essential oils from *Origanum floribundum Munby*, *Rosmarinus officinalis L.* and *Thymus ciliatus Desf.* against pathogenic strains of *Candidia albicans* isolated from milk of cows with clinical *mastitis.*

Herbal preparations used in mastitis treatment are becoming increasingly popular. Moreover, the popularity of organic cattle rearing systems is growing, but it requires the use of natural resources. A wide spectrum of administration possibilities (feed, injection and intramammary application, bolus) allows the use of herbs and natural plant extracts both as the basic form of *mastitis* treatment as well as an adjunct therapy [Wójcik *et al*. 2017, Mushtag *et al*. 2018].

Proteins and antimicrobial peptides in the treatment of *mastitis*

Treating mastitis can also involve the use of animal origin proteins. One example is lactoferrin, found in body fluids and secretions, e.g. milk, colostrum and saliva. Lactoferrin is a multifunctional glycoprotein with antiviral, antibacterial and antifungal properties [Pawlik *et al*. 2009]. Studies carried out by many researchers have demonstrated its efficacy in the treatment of cows with mastitis [Kutila *et al.* 2004, Suojala *et al.* 2013]. Lactoferrin was found to be effective against *E. coli, Pseudomonas aeruginosa, S. agalactiae* and *S. aureus* [Kutila *et al.* 2004, El Hafez *et al.* 2013]. Lee *et al.* [2004] investigated the *in vitro* susceptibility of pathogens causing mastitis (*E. coli, Klebsiella pneumoniae, S. aureus*, enterococci, coagulase-negative staphylococci, streptococci, *Prototheca zopfii* and yeast-like fungi) to lactoferrin and reported the highest susceptibility for *Prototheca zopfii* strains, while staphylococci showed different susceptibilities depending on the strain tested. The inhibitory effect of lactoferrin on the growth of *S. aureus* strains resistant to β-lactam antibiotics was demonstrated *in vitro* and *in vivo* by Lacasse *et al.* [2008].

Another protein used in the treatment of mastitis is β-lactoglobulin (β-LG), which is one of the main whey proteins in cow's milk. Chaneton *et al.* [2011] carried out *in vitro* tests to identify the antibacterial effect of this protein on pathogens causing mastitis. They demonstrated that β-LG inhibited the growth of *S. aureus* and *S. uberis*, depending on the concentration of the administered protein. The analysis for two protein variants, β-LG A and β-LG B, showed that β-LG A had stronger inhibitory properties. β-LG A combined with lactoferrin was also found to exert stronger antibacterial activity against *S. aureus*.

Lysozyme is a protein found e.g. in serum, milk, saliva and the egg white, which exhibits properties of a hydrolytic enzyme acting lytically on the peptidoglycan of bacterial cell walls [Gao *et al*. 2017]. Preparations containing lysozyme may be administered to cows during intravenous infusions [Blackburn and Polak 1998]. In their studies Malinowski *et al.* [2006] showed an increase in the efficacy for intravenously administered lysozyme dimer antibiotic treatment of mastitis caused by *S. dysgalactiae*, *S. uberis*, *E. coli* and *S. aureus*.

Antimicrobial peptides (AMP) found in all living organisms are basic forms of innate immunity [Bagnicka *et al.* 2011]. They show a killing effect against Gram-positive and Gram-negative bacteria, fungi, viruses and unicellular parasites [Brogden 2005]. Antimicrobial peptides that may be used to treat mastitis include defensin and cathelicidin [Cullor *et al*. 1991, Aono *et al*. 2006]. Studies indicate that in cows with clinical mastitis the level of these antimicrobial proteins increases in the glandular tissue as well as milk [Swanson *et al*. 2004, Zhao *et al*. 2015]. These proteins exhibit bactericidal properties against major mastitis-causing pathogens [Cullor *et al*. 1991, Tomasinsig *et al*. 2010]. A method to use AMP in the treatment of mastitis may include administration of synthetic forms of defensin and cathelicidin [Bagley *et al*. 2014].

The therapy using synthetic AMP peptides administered intramammary or in the form of injections is promising, but it is necessary to develop a method that will not reduce the effectiveness of AMP in the biological fluids of mastitic cows. High concentrations of salts, polysaccharides and anionic proteins, as well as the activity of the protease deteriorate the effectiveness of AMP therapy compared to studies conducted under laboratory conditions. In addition, another obstacle to the introduction of this treatment form is caused by a lack of commercial companies that produce synthetic AMP, thus reducing the costs of mastitis therapy with these peptides [Bowdish *et al*. 2005].

Use of bacteriocins in the control of pathogens causing mastitis

Bacteriocins are toxic substances produced by Gram-positive and Gram-negative bacteria which inhibit growth and kill related bacterial organisms. Due to their bactericidal properties, bacteriocins have been used as food preservatives for many years. The most popular bacteriocin used in the food industry is nisin and its antibacterial properties have also been demonstrated against pathogens causing mastitis in dairy cows [Ahmad *et al.* 2017]. Cao *et al*. [2007] investigated the *in vivo* effects of a nisin-based product and compared it to the effects of gentamicin treatment. Their experiments revealed that the product containing nisin had about 90% efficacy against pathogens, with the results being comparable to those recorded for conventional antibiotic treatment. Treatment with nisin eliminated 54.5% of infections caused by *S. aureus*, while the efficacy of antibiotics against this pathogen was 33.3%. Wu *et al.* [2007] demonstrated that the intraperitoneal administration of nisin resulted in a 90.1% cure rate of subclinical mastitis caused by *S. agalactiae,*50% for *S. aureus* and 58.8% for coagulase-negative staphylococci. The high efficacy of nisin against *Streptococcus* spp. strains isolated from dairy cattle in Poland was confirmed in studies by Kaczorek *et al.* [2017]. Those authors found that even a low concentration of nisin solution at 19.5 IU/ml may inhibit growth of *S. uberis, S. agalactiae,* and *S. dysgalactiae.* The high effectiveness of nisin in mastitis therapy has contributed to the US patent and FDA approval of two products: udder disinfection wipes based on nisin, Wipe Out®, and an intramammary preparation, Mast Out®, containing nisin (Immucell) [Ahmad *et al.* 2017].

Other researchers have investigated the potential use of lacticin 3147, a bacteriocin produced by *Lactococcus lactis* strains, in the treatment of mastitis [Crispie *et al.* 2005]. Klostermann *et al.* [2010] studied the effects of a teat dip containing the bacteriocin produced by *L. lactis* and found that a ten minute treatment eliminated 80% of staphylococcal strains, 90% of *S. uberis* strains and 97% of *S. agalactiae* strains compared to the control teats not treated with the dip containing *L. lactis.*

Research is continuing to identify new bacteriocins that may potentially be used in the treatment of mastitis. León-Galván *et al.* [2015] investigated the effects of five bacteriocins produced by *Bacillus thuringiensis* (Morricin 269, Kurstacin 287, Kenyacin 404, Entomocin 420 and Tolworthcin 524). *In vitro* tests demonstrated that these bacteriocins inhibited the growth of *S. agnetis, S. equorum, S. uberis, B. stationis* and *B. conglomeratum,* while the susceptibility of *S. aureus* varied depending on the tested strain.

Conclusions

Mastitis is the most common disease in dairy cows and alternative solutions to antibiotics have to be found for its treatment. The growing resistance to antibiotics in pathogens causing mastitis decreases the effectiveness of treatment and often leads to preterm culling of cows that cannot be cured, resulting in huge financial losses for dairy farms. Advanced *in vitro* and *in vivo* research on alternative solutions in mastitis treatment contributes to the patenting and first commercialisation of teat disinfectants and intramammary preparations, which in the future may have a significant impact in reducing antibiotic use in animal production and improving the effectiveness of udder inflammation treatment in dairy cows.

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