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Mini-Review: Alternative Therapies of Bovine Mastitis

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Abstract: Mastitis in dairy animals is a multietiological in nature and causing heavy economic losses worldwide. Over decades, much research has been conducted in the area of udder health. Although a variety of treatment and prevention protocols have been developed over the years, success rates have been variable and a true solution to the problem has not been found. Due to treatment limitations, research focus into the control of bovine mastitis has shifted to alternative therapies. In this paper alternative therapies are reviewed and the potential for their application are discussed.

Keywords: Clinical mastitis, Alternative therapies, Potential application.

1. Introduction

Mastitis in dairy cattle is a multifactorial disease with a long history. In addition to the associated impairment of welfare due to the pain, it is the most costly endemic disease in dairy herds with an average yearly incidence of about 28%. Among the economic loss components are the loss of milk production, treatment costs, extra labour and premature culling of chronically infected animals [1]. Moreover, mastitis represents a stress factor for the farmer.

Concerning human health with severe clinical *mastitis*, abnormalities of milk are easily observed and milk is discarded by the producer. Such milk normally would not enter the food chain. But when milk of cows with sub-clinical *mastitis*, *i.e*. with no visible changes, is accidentally mixed into bulk milk, it enters food chain and can be dangerous to humans. Although pasteurization is likely to destroy all human pathogens, there is concern when raw milk is consumed or when pasteurization is incomplete or faulty. Milk and other dairy products are frequently infected with with *S. aureus* According to [2] milk of infected animals is the main source of enterotoxigenic *S. aureus* of animal origin. For example certain *S. aureus* strains produce heat-resistant enterotoxins (toxins cannot be destroyed by heating or drying), which cause nausea, vomiting and abdominal cramps when ingested by humans and are responsible for staphylococcal food poisoning outbreaks [3, 4] .

2. Materials and Methods

. Potential problems

About 95% of all infections are caused by *Streptococcus agalactiae, Staphylococcus aureus, Streptococcus dysgalactiae*, *Streptococcus uberis*, and *Escherichia coli.* The remaining 5% are caused by other organisms. Contagious organisms are spread by hands, milking units, etc. They include *S. agalactiae*, *S. aureus*, *S. dysgalactiae*, and mycoplasma.

, rather than at the end of the paper. Number Over decades, much research has been conducted in the area of udder health. Although a variety of treatment and prevention protocols have been developed over the years, success rates have been variable and a true solution to the problem has not been found. Differences in mastitis prevalence rates between farms are large [5,6] .

3. Alternative and Novel therapies for control of mastitis

3.1. Development of vaccines

Due to these treatment limitations, research focus into the control of bovine mastitis has shifted to alternative therapies such as the development of vaccines [7]. Vaccines for *S. aureus* have produced varied levels of success. This has been a result of the type of vaccine used, adjuvants and other factors such as age of the cow and environmental conditions [8].

The bovine mammary gland can be a significant reservoir of enterotoxigenic strains of *S. aureus.* Two different types of toxin with super-antigen activity can be produced: enterotoxins and toxic shock syndrome toxin (TSST-1). The staphylococcal enterotoxins (SEs) have been divided into five serological types (SEA, SEB, SEC, SED, and SEE) on the basis of their antigenic properties [9]. The strains producing the staphylococcal enterotoxin type C (SEC) have been widely isolated from *mastitis*-afflicted cows [10, 11,12]. Recently, the occurrence of new types of SEs (SEG to SEJ) has been reported [13,14]. However, the relationship between these new SEs and bovine *mastitis* has not been sufficiently clarified. A

recent study has shown that a commercial bacterin (vaccine comprising killed bacteria) did not result in effective from three bacterial strains with different haemolysis patterns added to the bacterin which resulted in greater than 50% protection in the experimental challenge [16].

DNA and recombinant protein vaccines have been tested for the main factors of *S. aureus* virulence that are *aureus* related to infections in the mammary gland [17,18] .
However, owing to the importance of pathogenity of toxin formation of *S. aureus* for udder remains unclear, due to the wide variety of vaccines available against *S. aureus* and the variable clinical results associated with each, there remains no general consensus on which immunotherapeutic protocol is the most efficient.
Given today's public health and food safety concerns regarding antimicrobial resistance and antibiotic residues in dairy products associated with treatment of diseases like mastitis, approaches to enhance the cow's immunity to prevent udder disease, improve milk quality, and thus minimize use of antibiotics has gained considerable attention. Yet, for a variety of reasons, vaccines developed for the prevention and control of mastitis have achieved only limited success. The multiplicity of pathogens capable of causing mastitis and knowledge of mammary gland immunology, bacterial virulence factors, and mechanisms of pathogenesis are factors that have hindered development of effective mastitis vaccines. However, some progress has been made in these areas in the last decade or so.

3.2. Bacteriophage therapy

Bacteriophage therapy has been exploited for the control of bacterial diseases in fauna, flora and humans. However, the advents of antibiotic development lead to a cessation of most phage research. Recently, the problem of antibiotic resistance has rendered many commonly used antibiotics ineffective, thereby renewing interest in phage therapy as an alternative source of control [19].
Phage therapy can provide a sustainable, organic means of mastitis control with little to no deleterious effect on the surrounding environment or the affected animal itself. Several studies have delved into the field of biocontrol of bovine mastitis using phages. Results are variable. However, some phage-based products have been commercialized and are available on the market. The unequivocal fact that emerges from research findings so far is that phages may be the next avenue of control for bovine mastitis and other problematic bacterial diseases.
phage therapy was applied to different disciplines ranging from human and veterinary medicine to agricultural settings [20,21] and was initially used to successfully treat a variety of diseases ranging from dysentery, typhoid and paratyphoid fevers, cholera and pyogenic urinary tract infections

3.3. Stem/progenitor cells therapy

A study of Capuco et al., [22] have been tried to establish *in-vivo* expansion of bovine mammary stem cells using an intramammary infusion of xanthosine to improve the growth of mammary epithelial cells. Two major cell types, epithelial and myoepithelial stem/progenitor cells are of considerable therapeutic interest in mammary gland tissue. These can support the development of a vascular network (endothelial and smooth muscle cells) within the mammary gland. Unfortunately, the current therapeutic strategy can not able to protection from new infections of *S. aureus* [15]. Better results have been obtained with a toxoid produced improve or revert the post-mastitis structural damage more than 50% in the mammary gland.
[23] Sharma and Jeong , presented a review focused the insight into the possible application of various stem/progenitor cells including mammary stem cells and other origin adult stem cells in the repair of post-mastitis structural defects in the dairy animals. Due to the self-renewal ability and the subsequent generations with variable degrees of differentiation capacities has given the impact of these cells in therapeutic research and applications. Therefore, the significant potential of these progenitors could be used for generation of tissues that can potentially replace or repair diseased and also the damaged tissue like epithelial, myoepithelial and or cuboidal/columnar cells in the udder.
Although from last few decades, the stem cell techniques are being used as a therapeutic tool for regenerative medicine in human but it is still lacking in the treatment/corrections of various challenging ailments in livestock such as the mastitis. Moreover, a more precise study has needed to identify bovine mammary gland stem/progenitor cells markers for isolation of specific cell populations for further application in udder repair.

3.4.Electrochemically activated water "Anolytes" and Silver nano-particles

[24] Kaoud and Yosseif , conducted a study on 120 mastitic buffaloes were having mixed infection with *E. coli, Staph* aureus and *Strept.agalactae*. They applied 6 lines of treatment; the diseased animals were classified into 6 groups (20 each).
The first group received local treatment by intramammary infusion of ceftiofur hydrochloride; the second one received systemic treatment by I/M injection of both enrofloxacin and I/V injection of carprofen as an immunomodulator drug and the third one received a combination of both local (intramammary infusion with ceftiofur) and systemic treatment (I /M injection of both enrofloxacin and I /V injection of of carprofen . The forth group received local treatment by intramammary infusion with Neutral-Anolyte. The fifth group received local treatment by intramammary infusion with AgNPs suspension. The sixth group received both local treatments by intramammary infusion with Neutral-Anolyte and received systemic treatment (I /M injection of both enrofloxacin and I /V injection of carprofen .
The cure rate was 60 % for the first group, 80 % for the second and third group. The fourth and fifth group both were 60 %, while 100% in the sixth group.
EnvirolyteNeutral-Anolyte (1\500) and AgNPs were induced similar curing rate (60%) for 5 days intramammary infusion treatment.
Electrochemically activated water "Anolytes" demonstrate universal action, i. e. produce damaging effect on all major systemic microbial groups (bacteria, fungi, viruses and protozoans), being harmless for the tissue cells of higher organisms, i. e. somatic animal cells making up a multi-cellular system. Microorganisms do not produce such substances in the process of their life activity and have no powerful anti-oxidant defense system, which is why electrochemically activated biocidal solutions are highly toxic for them. Biocidal substances in electrochemically activated solutions commonly used as antiseptic or chemotherapy agents are not toxic for human somatic cells, since 50-95% of them are represented by

oxidants similar to those produced by the cells of higher organisms.

The unique physiochemical properties of the nano-particles combined with the growth inhibitory capacity against microbes has led to the upsurge in the research on nano-particles and their potential application as antimicrobials. The mechanism of antibacterial effect of silver nano-particles has been reported in (4) interference with cellular S-containing compounds, and (5) intracellular ROS accumulation [26] [27,28,29,30 ,43,25] . That several of these events might act together to result in cell death is probable, but the specific processes and interactions required for toxicity have not been fully confirmed.

A. *The released silver ions and generate ROS; interact with membrane proteins affecting their correct function; accumulate in the cell membrane affecting membrane* the literature [25], which suggests that the particles are bactericidal. Several possible modes of action are discussed in the literature on nano-Ag effects on bacteria and fungi. These are (1) membrane disruption through direct attachment of the nanoparticle to the bacterial membrane, (2) cellular invasion and enzyme disruption by nanoparticles, (3) changes in cell membrane permeability *permeability; enter into the cell where it can generate ROS, release silver ions and affect DNA. Generated ROS may also affect DNA, cell membrane and membrane proteins and silver ion release will likely affect DNA and membrane proteins. [31,32]*.

section) should have the first line indented about 3.6 mm (0.14").

Competing interests

The author has declared that he has no competing interests.

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