Bactericidal potential of lactic acid bacteria against pathogenic *Streptococcus pneumoniae* from ophthalmic infections- A systematic review

Running title: LAB as Antibacterial tool against pathogns

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Abstract

Background: In recent years, eye diseases have become increasingly common medical issues, partially due to the rise in contact lens users. Conditions such as conjunctivitis (commonly known as pink eye), keratitis, corneal ulcers, and trachoma are spreading widely across the globe. **Methods:** Different search engines were used to collect the data relating to ophthalmic infections and associated pathogens. **Results:** The bacterial pathogens identified as causes of eye infections include *Staphylococcus* sp., *Streptococcus* sp., *Neisseria* sp., *and Bacillus* sp., which primarily lead to corneal diseases. In the United States, the annual incidence of microbial keratitis is approximately 30,000 cases. While bacterial eye infections are effectively treated with antibiotics that can eliminate the pathogens, they do not reverse the damage already inflicted by bacterial toxins. Lactic acid bacteria (LAB) derived from traditional fermentation processes are recognized for their antibacterial properties and are effective against both Gram-positive and Gram-negative bacteria. The dominant LAB found in Sichuan pickles is *Lactobacillus* *plantarum*. Bacteriocins are proteinaceous or peptidic toxins produced by bacteria to inhibit the growth of similar or closely related bacterial strains. Antimicrobial agents play a crucial role in reducing the global burden of infectious diseases. However, as resistant pathogens develop and spread, the effectiveness of these antibiotics diminishes, posing a serious threat to public health. This resistance is increasingly prevalent across all types of antibiotics, including critical last-resort medications. **Conclusion:** A collaborative scientific approach that encompasses various disciplines is necessary to unlock the vast potential of bacteriocins in shaping the microbiome. Furthermore, there is a need for the development of new antimicrobial agents with optimized pharmacokinetic and pharmacodynamic properties that exhibit low toxicity, high efficacy, and a reduced risk of resistance development.

Key words: Antibiotics, Antimicrobial agents, Bacteriocins, Pathogens, *Plantrum* and microbiome.

Objectives

The objective of current review is to understand the eye infection risk due to S*treptococcus pneumoniae* and to inhibit the growth of *Streptococcus pneumoniae* by using naturally occurring bacteria such as *Lactobacilli* instead the use of antibiotics as excessive use of antibiotics has different side effects

Introduction

In recent years, eye infections have become a prevalent medical concern, largely attributable to the rising number of individuals using contact lenses. The symptoms of eye infections can vary widely and may include eye pain, redness, sensitivity to light, blurred vision, and excessive tearing [40]. One common type of eye infection is bacterial conjunctivitis, which affects the mucous membranes lining the inner surfaces of the eyelids and the sclera. In the United States, the estimated incidence of bacterial conjunctivitis is about 6 million cases annually, resulting in a significant social and economic burden, with costs totaling around USD 857 million each year due to medical expenses and lost productivity [27]. Although keratitis occurs less frequently than conjunctivitis, it presents a serious medical issue that requires immediate attention and can lead to vision impairment if left untreated. The annual incidence of microbial keratitis in the United States is approximately 30,000 cases. Ghafoorianfar et al. (2020) indicated that bacterial keratitis is the most prevalent form and can be caused by various microbes, including *S. aureus*, *S. pneumoniae*, and *P. aeruginosa*.

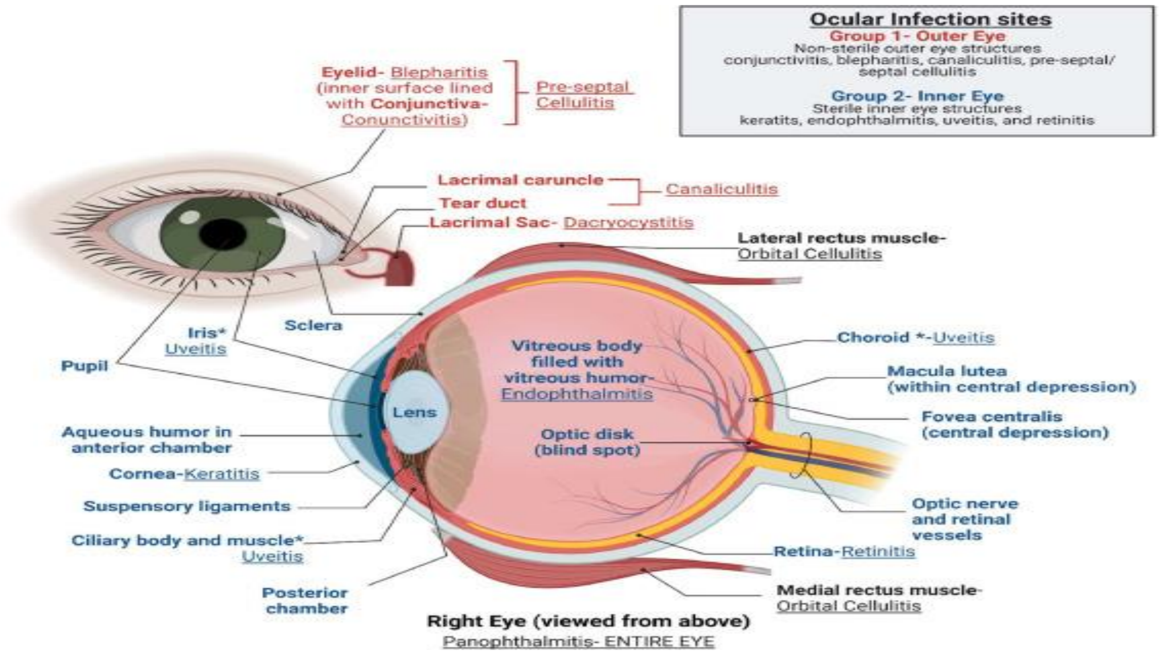

Fig. 1. Anatomy of the human eye and surrounding tissues with associated infection diagnosis, grouped by clinical categorization [37].

Symptoms of Eye Infections

Eye infections such as conjunctivitis (often referred to as red or pink eye), keratitis, corneal ulcers, and trachoma are widespread around the globe. These infections occur when harmful bacteria invade parts of the eye or the surrounding area [1].

Ocular Infections Caused by *S. pneumoniae*

S. pneumoniae is a significant pathogen responsible for numerous diseases, including pneumonia and various eye disorders such as conjunctivitis and keratitis [36]. Streptococci are a genus of nonmotile, Gram-positive cocci that typically range in size from 0.5 to 2 µm and can be organized in pairs or chains, depending on the direction of bacterial binary fission. This genus belongs to the Bacillus phylum within the order Lactobacilli and the Streptococcus family [15]. These bacteria are primarily facultative anaerobes and are categorized based on their hemolytic properties, with alpha-hemolytic strains causing partial hemolysis of red blood cells [12].

Virulence Factors of *S. pneumoniae*

The pathophysiology of *S. pneumoniae* is well-established, with critical virulence factors such as the polysaccharide capsule, pneumolysin, neuraminidase, and zinc metalloproteinases being identified as contributors to ocular disease [32]. Additionally, key bacteria from the viridans streptococci group, including cytolysins and proteases, have been documented, though further research is needed on other streptococcal species. These virulence factors frequently play a role in the onset of infections [23].

The most prevalent pathogens associated with eye infections in children include *S. pneumoniae*, *S. epidermidis*, and *P. aeruginosa*. Common bacterial isolates from these infections have been identified as *Staphylococcus spp*., *Streptococcus spp*., *Neisseria spp*., and *Bacillus spp.*, which are often associated with bone pain [6]. All pathogenic isolates were found to be sensitive to a range of compounds, except for *Streptococcus spp*. (BS1), which exhibited resistance solely to 3-nitroaniline (SAHC-11) [7]. The epidemiology of ocular diseases is crucial as it sheds light on the behavior of various pathogens within the eye. Species such as *S. aureus* and *S. pneumoniae* produce proteins capable of damaging the cornea, potentially resulting in vision loss, particularly among contact lens users [40].

Clinical manifestation

Use of Antibiotics

Antibiotics are often referred to as "time warp" drugs, as they are typically administered for short durations and specific conditions [34].These medications primarily combat bacteria by disrupting proton movement across cell membranes, which diminishes the bacteria's capacity to generate or store energy, inhibits protein synthesis, and affects cell wall synthesis, among other mechanisms [30]. Common antibiotics, including gentamicin, erythromycin, tetracycline, and ampicillin, are frequently utilized to manage eye infections. While antibiotics can effectively kill bacteria, they do not repair the damage inflicted by bacterial byproducts [10]. There is an increasing presence of antibodies within the ocular system, which is believed to correlate with a rise in ocular isolates resistant to antibiotics [8]. In particular, eye infections caused by Gram-positive bacteria demonstrate a higher level of antibiotic resistance. Moreover, some patients may experience adverse effects such as punctate epithelial keratitis [19].

Table 1. The most effective antibiotics against *Streptococcus pneumoniae* isolates [25].

Antibiotics	No of sensitive isolates	Rate (%)
Vancomycin	201	100
Clindamycin	158	78
Erythromycin	112	54
Cotrimoxazole	81	40
Cephalothin	67	33
Penicillin	60	30

Antibiotic-Resistant Pathogens

Multidrug-resistant (MDR) bacteria are defined as those that exhibit resistance to multiple antibiotics. The emergence and spread of MDR infections have emerged as a significant global health concern [20], posing serious risks to patient safety. Antibiotic resistance is often linked to incomplete courses of antibiotic treatment, leading to diseases that can withstand one or more antibiotic agents [29]. Additionally, genetic mutations and the vertical and horizontal transfer of resistance genes among organisms play crucial roles in the development of antibiotic resistance. This growing threat from antibiotic-resistant bacteria endangers public health, with an alarming rise in resistance rates to numerous antibiotics, including those considered last-line treatments [3]. Consequently, there is an urgent need for alternatives to antibiotics, prompting a re-assessment of traditional medical approaches [38]. In the United States and Europe, antibiotic resistance is responsible for approximately 50,000 deaths annually, with a global estimate exceeding 700,000 fatalities [25]. If no significant measures are implemented to combat this issue, projections suggest that by 2050, 10 million lives could be lost each year due to antibiotic resistance [9].

Clinical manifestation

Lactic acid bacteria a source of antimicrobial agent

The rise in drug resistance highlights the urgent need for alternative treatments [24]. Lactic acid bacteria (LAB), recognized for their probiotic and anti-inflammatory benefits, show great potential [21]. LAB, which are isolated during traditional fermentation processes, have demonstrated antibacterial properties that are effective against both Gram-positive and Gram-negative bacteria. This broad spectrum of activity enables lactic acid bacteria to serve as preservatives in various food products [5]. While their antimicrobial effects against intestinal infections are well established, recent research has also explored their efficacy against respiratory and ocular infections [13]. Notably, two significant groups of these bacteria belong to the genera *Lactobacillus* and *Bifidobacterium*, alongside numerous other probiotic strains [2]. Furthermore, studies have shown that the composition of lactic acid bacteria in different areas of Sichuan Province is complex [22].

Antimicrobial activity

Antimicrobial substances typically suppress the growth of pathogens through competitive exclusion within the intestinal lumen. Lactic acid cultures produce compounds such as bacteriocins, surfactants, hydrogen peroxide, organic acids, and bacteriocin-like inhibitory substances to impede the growth of pathogens [35, 26]. These results suggest that the suppression of pathogenic strains in low pH supernatants is primarily attributed to the generation of acidic compounds, including acetic acid, propionic acid, and lactic acid. Additionally, further research on varying pH levels is necessary to validate the antimicrobial capabilities of the isolated cultures. [28].

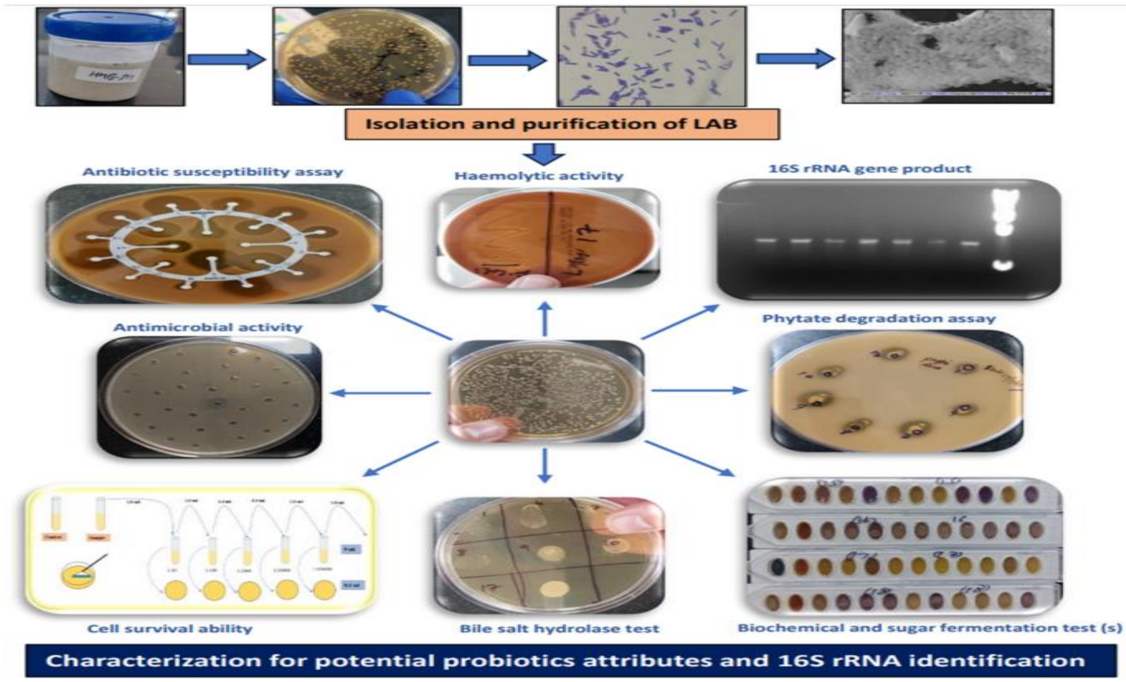

Fig 2. Isolation and purification of LAB [31].

Antimicrobial Properties of Bacteriocins Produced by LAB

Bacteriocins are protein or peptide toxins generated by bacteria that inhibit the growth of similar or closely related bacterial strains [4]. Bacteriocins sourced from Gram-positive bacteria, particularly lactic acid bacteria (LAB), have been extensively studied for their biosafety and numerous industrial applications [18]. These antibacterial peptides produced by various lactic acid bacteria are frequently utilized to suppress the growth of other species or strains with comparable nutritional profiles. Unlike most antibiotics, bacteriocins are protein-based preparations that are quickly broken down by proteases in the human digestive system. Their ribosomally synthesized peptides allow for modifications that can enhance their efficacy and range of action.

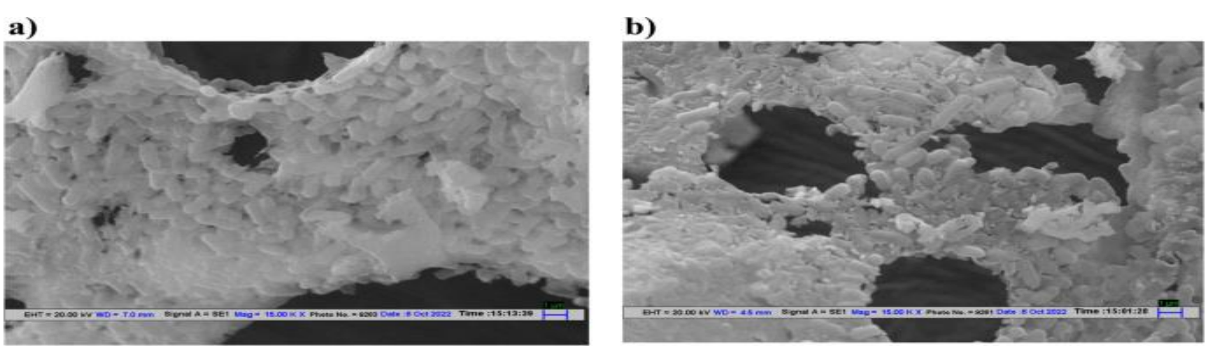

Fig 3. Scanning electron micrographs (15.00 K X) of lactic cultures. a *Limosilactobacillus fermentum* MS005. b *l. plantarum* MS007 [31].

Discussion

The human microbiome has a significant influence on overall health in various ways, involving not only beneficial bacteria but also pathogenic strains that can invade normally sterile tissues and trigger infectious [16]. Streptococci have been linked to several health conditions, such as diabetes and various forms of endophthalmitis, represented by case proportions of 10.3%, 37.5%, 29.4%, and 57.1%, respectively [11]. Pneumolysin, a cytolytic protein generated by *S. pneumoniae*, possesses multiple properties that may play a critical role in ocular diseases associated with pneumococcal infections [33]. *S. pneumoniae* stands out as a key virulence factor within ocular disorders that can lead to severe outcomes like blindness. The implementation of pneumococcal conjugate vaccines (PCV) has led to a decline in cases of pneumonia and invasive pneumococcal disease, but its effects on ocular infections remain noteworthy. The research by Asfaw *et al*., [2024] indicates that various factors, such as the selective pressure of PCV-13 and the specific behaviors of host niches, might influence the ocular pneumococcal population structure [17]. Over the last 20 years, the resistance rates of *Streptococcus pneumoniae* to penicillin have reached 20% to 30%, and resistance to macrolides and azalides has risen to 25% to 35%. Moreover, 20% to 30% of H. influenzae strains are known to produce beta-lactamase, which provides resistance to ampicillin. The growing antibiotic resistance among ocular bacteria raises significant concerns, as their resistance to most antibiotics has escalated [39]. Specific strains of *Lactobacillus*, such as *L. plantarum* (DSM20174) and *Lactobacillus salivarius* (DSM20555), have been employed to help mitigate microbial infections [26]. Bacteriocins were successfully isolated from MRS cultures of lactic acid bacteria through 1N HCl permeation precipitation and were tested against various bacterial strains Yap *et al*., [2022]. Remarkably, bacteriocins derived from *Lactobacillus acidophilus* (DSM20079) demonstrated the strongest antibacterial properties against a wide range of bacteria, with *Lactobacillus salivarius* (DSM20555) showing the highest efficacy against methicillin-resistant *S. aureus (Chlamydia pneumoniae)* [17].

Findings

Lactic acid bacteria (LAB) species, including *L. rhamnosus*, *L. plantarum*, and *Lactobacillus casei*, have been shown to significantly inhibit the growth of *S. pneumoniae* in in vitro studies. The production of lactate and bacteriocins may play a crucial role in this inhibition. Preliminary clinical investigations involving patients with infectious diseases have yielded favorable results for LAB treatments, indicating their potential as a safe and effective alternative to traditional antibiotics.

Challenges

While LABs present a promising alternative for addressing *S. pneumoniae* infections, numerous obstacles exist. These challenges include identifying the most effective LAB strains for specific diseases, developing LAB formulations that are both stable and effective for ocular applications, and ensuring their safety for such use. Future studies should prioritize: evaluating the true bactericidal effects of LAB against *S. pneumoniae*, conducting large-scale clinical trials to validate the safety and efficacy of LAB treatments, investigating the synergistic potential of LAB in combination with antibiotics to enhance clinical outcomes, and pursuing clinical trials utilizing molecular techniques for assessing anti-inflammatory drugs in ocular disease contexts.

Novelty of such type of studies:

This review highlights the research studies on eye infections induced by *S. pneumoniae.* Ocular diseases present distinctive challenges and are particularly significant for the advancement of antibiotic strategies aimed at addressing these issues. The study's uniqueness lies in its combination of microbiology, food science, and ophthalmology. This multidisciplinary approach enhances our understanding of how nutrition and disease intersect concerning eye health.

Expected Results of these studies:

By conducting type of studies discussed in our review, different types of ophthalmic infection can be diagnosed and treated on better level. These steps include:

• Identification and characterization of lactic acid bacteria derived from natural products.

• Confirmation of the in vitro bactericidal properties of *Lactobacillus* against *S. pneumoniae.*

• Identification of bacteriocins and the genes encoding them that contribute to the bactericidal effects of lactic acid bacteria.

Conclusion:

Lactobacilli present a promising alternative to traditional antibiotics for treating infections caused by *S. pneumoniae*, including those affecting the eyes. Their inherent antibacterial traits, coupled with their safety profile, render them a viable option for future therapies. Ongoing research and development could position lactic acid bacteria as a significant player in enhancing immune system responses.

Declarations

All authors listed in paper have made important contributions and there is no conflict of interest among authors.

Supporting Information

None

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