Review Article

Therapeutic potential of bacteriocin like inhibitory substances against different disease conditions

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Abstract

Bacteriocin like inhibitory substance produced in many starter cultures and milk products has the significant potential to improve the quality of diverse edible food stuffs. Many authors confirmed that the Nisin produced by many lactic acid bacteria used in many food items to stop *L. monocytogenes*. The data resulted from the antimicrobial substances establish determined that the peptides existence towards indicator bacteria might be considered as BLIS because they have the bacteriocin like compounds, but they did not until now been characterized for encoding nucleotide sequences and amino acid. Antibiotic resistance result from the extreme utilizing of therapeutic agents in animals and humans is an international issue. This concern has diverted the concentration of researchers to discover another key answer for these antimicrobial agents. Bacteriocin-like inhibitory compounds are currently considered as the new substitute for antibiotics to cure numerous diseases and infections. Bacteriocin like compounds obtained from Gram-positive bacteria is present in scientists' deliberation due to their various range of antimicrobial action. This review focuses on the therapeutic potential of bacteriocin-like inhibitory substances against different disease conditions.

Keywords: Antibiotic resistance; Therapeutic agents; Bacteriocin; Inhibitory substances

Introduction

Bacteriocin like compounds was repressed by the advancement of other bacteria with a killing action. Numerous lactic acid bacteria created varied bacteriocins like compounds. Bacteriocin like compounds formed LAB

were frequently regarded as secure and helpful to inhibit the growth of pathogens. They are commonly worn as cultures in food industries. This report revealed that the screening of 699 LAB was separated from wooden surfaces, cheeses, and raw milk to

create BLIS, compared by two methods. The antimicrobial action of LAB and their protein character was conducted by the agar diffusion agar and spot lawn assay and the compassion to amylolytic and lipolytic enzymes. The pathogenic bacteria were *L. monocytogenes*, *Staph aureus*, *E. coli*, *Salmonella typhii* 223 strains originated to stop the development of *L. monocytogenes* utilizing the spot lawn assay, but 37 were established by well diffusion assay method [1].

Characteristics of *Lactobacillus*

Most of the bacteriocin like properties is related to *Lactobacillus* and *Bifidobacterium* spp. However, it is regarded as the employ of different strains to isolate bacteriocin-like inhibitory substances. Humans should be as usual residents of a healthy tract and stay healthy in the upper digestive tract and capable of presenting and growing in the intestine. They can resist the bile salt, acidic pH and secure for human consumption. These also produce antimicrobial compounds such as bacteriocin-like inhibitory substances. The lactic acid bacteria are high-quality and safe records and not concerned with diseases. The most common utilization of bacteriocin-like inhibitory substances is *Lactobacillus* spp, *Bifidobacterium* spp, and *Lactococcus* spp. They were regarded to be safe as GRAS [2].

Lactobacilli are characterized as Gram-positive facultative bacteria. They are non flagellated rods, non-spore-forming, and coccobacilli bacteria. They are strictly fermentative to ferment lactose sugar and many other monosaccharide sugars mainly into lactic acid with homofermenter, and these ferment into lactic acid carbon dioxide and ethanol by heterofermenters. *Lactobacillus* is mostly fine used in the diet; thus, they assert that bacteriocin-like inhibitory substances include *L. acidophilus*, *L. casei*, *L. delbrueckii* .*L. Plantarum*, *L. fermentum* [3].

On the other hand, the central part calculated the widely used starter culture in the dairy industry. *Lactobacillus acidophilus* belongs to the homofermentative grouping of *Lactobacilli*. *L. acidophilus* bacteria are non-motile, non-spore-forming, and non flagellated. Gram-positive, facultative, rod-shaped bacteria range from 0.6 to 0.9 μm in width and 1.5 to 6.0 μm in length. These cells may emerge singly or in pairs as well as in small chains. The optimum bacterial growth found at 35-40°C however, these may tolerate high temperature as 45°C temperature. The most favorable pH for bacterial growth is between 5.5-6.0 [4].

Characteristics of *Bifidobacterium* Spp.

In the life of the animal and human, *Bifidobacteria* is mainly frequent in intestinal microflora. They significantly increased in number in the stool after birth and breastfeeding. They are contributing 6-35% of adults prevailing inside the colon of the intestinal. However, the number of these bacteria reduces over time. *Bifidobacterium* are Gram-positive rods, non-spore former, non-motile they are bent and bars shaped with a diversity of small chain forms, shaped of club broads and greater partis of V or Y shape are several species are anaerobic, *Bifidobacterium* can also bear some extent of oxygen [5].

Bifidobacterium spp generates organic acid, e.g., lactic acid & acetic acid; under the standard fermentation procedure, such bacteria could ferment carbohydrates like galactose, lactose, and fructose because they contain an enzyme called Fructose-6-phosphate phosphoketolase F6PPK [34]. The *bifidobacterium* spp counted because it has a precious outcoming on the human host physical condition, including the production of many nutrients. The most favorable pH for development while other bacterial effects on six to 8 with no growth at pH 4.6-5.5 or below and high in pH while *Bifidobacterium lactis* had revealed capable growth at pH 4.2. The

most favorable temperature for growth ranges from 37 to 41°C with little growth above at 46°C and below at 25°C temperature [6].

Mechanism of Action of Bacteriocin like inhibitory substances

Gram-positive bacteriocin's mechanism, like inhibitory substances produced by bacteria, has been deliberated via numerous researchers in this era. The bacteriocinogenic microbes are measured to sustain the host's physical condition [7].

Various scientists had studied that how bacteriocin, like inhibitory substances producing microorganisms, work. Many modes of action from those surveyed are demanding to elucidate that these bacteria might defend the host as of the internal disorders and several new diseases. The possible bacteriocin action like inhibitory compounds is discussed precisely below in brief [8].

Antimicrobial Effect of BLIS on Pathogens via secretion of inhibitory compounds

Lactic acid bacteria include the microbes after forming antagonistic compounds like bacteriocin-like compounds, ammonia, H₂O₂, bacterial enzyme & numerous further organic acid. All the combinations are regarded as therapeutic agents that include Gram-negative and Gram-positive pathogens [9].

Blockage of attachment sites

BLIS and pathogens have always remained in a fight. BLIS is associated with the areas concerned with correcting pathogen intestinal epithelial site [10].

Fight of nutrients

These are several studies in vivo conditions, the pathogenic bacteria that could stop pathogen growth by utilizing many nutrients that pathogens might require [11].

Motivation for the immune system

BLIS can motivate the same and nonspecific and specific immunity to defend the host

from intestinal disease and many other pathogenic microorganisms. The mode of action is not identified. However, it was considered definite cell membranes components and may act as an adjuvant to stimulate humoral immunity [12].

Deprivation of toxin receptor

BLIS could be degrading the toxin receptor on the intestinal mucous membrane; it could expose it and save against *S.boulardi* and *C.difficile* intestinal problems [13].

Effect on the metabolic process

BLIS microorganisms are particular to have a possible effect on the metabolic process. These can increase the mode of action of the host metabolism. The BLIS also decreased bacterial enzyme action and limited the creation of ammonia. All these assets feed improved the intake and digestion process in humans [14].

Non Immunological actions

One more possible mode of action of BLIS is the non-immunological effect in enhancing GIT security barriers. These can enlarge and nourish intestinal permeability and changed gut microbial ecology. Similarly, several other available modes of action are inhibition of toxin, shrinking of virulence, and decreased gut pH [15].

Selection standard for BLIS

These advantageous assets planned to apply a potentially victorious BLIS strain have a numeral of attractive properties. The subsequent criteria are for BLIS properties [16].

Bacteriocin like inhibitory substances strain properties

Bile salt and acid tolerance

Another significant role of BLIS is with oral consumption because they are the beneficial bacteria that may continuously present in the intestine, maintaining the epithelial wall's thickness and other useful metabolism action [17].

Attachment to mucosal site

Significant to reached in the immune system, by the adhesion of mucosal surface fights with pathogenic bacteria, maintaining the metabolic process, and avoiding the pathogens to bonding and colonize on the epithelial cell membrane layer [18].

Clinically validated and accepted health effect

Precisely the detection and purification of BLIS bacterial are considered documented safe. No fight and no breakage of the intestine mucosal site occurred [19].

Good technological properties

BLIS was selected into four basic categories. It includes proper, competition recital, technical suitability, and functionally. BLIS bacterial species that are owing these standards should obtain competent results on human fitness by these functional BLIS producing bacteria. Some primary selection of criteria is mentioned below [20].

Antimicrobial actions

Antimicrobial action is single of the excellent standard for the identification of BLIS. Lactic acid bacteria produce certain organic substances such as acetic acid, lactic acid, diacetyl, propionic acid, hydrogen peroxide, low molecular weight carbon dioxide, and bacteriocin-like inhibitory substances showed antimicrobial effects against different pathogenic microorganisms. Different LAB bacterial species significantly overstate the formation of BLIS. Nisin is formed by *L.lactis* from the recognized bacteriocin-like compounds and is acceptable to utilize in various fermented food-related products in the dairy industry [21].

The isolated BLIS, such as from *Bifidobacteria* and *Lactobacilli*, were assayed that they have antimicrobial action towards the indicator pathogenic microorganisms like as *Listeria spp*, *E.coli*, *Staphylococcus spp*, and *Pseudomonas spp*. Antimicrobial activity of *Lactobacillus spp* is considerably talented in inhibiting gram-

negative and some gram-positive bacteria in vitro conditions. Similarly, *B. bifidum*, *Bacillus subtilis*, *B. thuringiensis*, and *Lactococcus lactis* also exhibit antimicrobial activity against the pathogenic bacteria [22]. Similarly, in another study, 8 LAB strains produced bacteriocin-like inhibitory substances obtained from fermented milk products. Those were checked for the antimicrobial action towards the pathogenic Gram-positive and Gram-negative bacteria *Bacillus cereus*, *Mesenteroides Enterococcus faecalis*, *Pediococcus spp*, *Escherichia coli*, *Staphylococcus aureus*. *Lactococcus spp* and *Lactobacillus fermentum* showed their inhibitory activity. The zone of inhibition was obtained between 8- 12 mm, which was an efficient one. *Lactobacillus fermentum* shows a broad area of inhibition around 12mm *mesenteroides subsp. Mesenteroides* [23].

Acid and bile tolerance

BLIS bacterial strains are used in the dairy products, which reached the lesser intestinal area via the oral cavity. And the BLIS should be disparate to the enzyme in the mouth cavity. The further voyage departure on inside the stomach and goes in the upper intestinal area, including bile salt. In this phase, bacteria be supposed to have the potential to combat the absorption mechanism. It is recorded as the initial entrance to secrete from stomach acquire 2 hours. BLIS compounds require to be conflicted to the stomach's traumatic conditions at pH 2.0 to 3.0, which grasp bile salt [24].

To detect the bile salt-resistance and acidic pH of *Bifidobacteria spp* be separated stool samples of humans and be studied and screened for development at pH 4.5. After this isolation of bacteria, they were examined for continued existence cerate at different pH 2.5 and 7.5 [25].

The beneficial effects of Bacteriocin like inhibitory substances on health

There is an abundance of analysis researching the practical aspects of foodstuffs on human health. So, numerous studies reported that have been incompleting, and some of them can be regarded as bacterial strains for bacteriocin production like inhibitory compounds. These health-related effects can be listed below [26].

- Control of lactose intolerance.
- Increasing immunization.
- Prevention of colon cancer in animals.
- Lowering of cholesterol level
- It is decreasing of blood pressure in humans as well as animals.
- Limit the different bacterial inflammation.
- The decrease in the allergic reaction.
- Advantageous possessions on the metabolic process.
- Turn down of *Helicobacter pylori* infections.
- Suppression of pathogens due to antimicrobial activity.
- Hindrance of osteoporosis infection.
- The eagerness of urogenital infections in humans.

Lactose Intolerance

The chief probiotic property is to improve the digested by lactose through a bacterial enzyme called β galactosidase. Similarly, the lessening of gastric juice by fermented milk products, for example, butter and yogurt. The β galactosidase enzyme activity in BLIS is in a vast range. It has vigilant mutually the enzyme activity of strain and the action lack in the end manufactured goods by consuming lactose, which caused lactose intolerance [27].

Immune modulation and response by BLIS

The bacterial carcinogenic property on the immune system is beneficial. Equally, the process is not well known. The human analysis showed that BLIS producing bacteria have positive actions on the resistant

structure to their host. [28] considered that fermented foodstuffs' utilization contains *bifidobacteria spp* and *Lactobacillus acidophilus* and might change the human immune responses. It is provided to volunteers via fermented products and a curd period of 3 weeks, indicating that *salmonella* was injected to copy the enteropathogenic diseases. After two weeks, the serum-containing IgA *Salmonellatyphii* in the test group was > 4 folds. The whole level of serum IgA developed. The outcome showed which may keep on acting in the GIT and may be dynamic the immune system.

[29] cultivate the mice with *Lactobacillus* species in the curd. After that, macrophages improved the secretory IgA level in the mice.

Cholesterol reduction

Many studies revealed that BLIS has the potential to reduce cholesterol. There are two types of hypotheses demanding to demonstrate the mechanism. One is that the bacteria may bind to the cell membrane, and the other conjugated with the bile salts cause hydrolysis bile salt by specific enzymes which exerted chronological cholesterol collapses [30].

Balance of gastrointestinal microflora

BLIS produces microbes found in the intestine tract and oral cavity of healthy human beings and supports the body to eliminate the entering of harmful microorganisms in humans' bodies. Due to the dominance of antibiotic treatments, which killed the functional microorganism and pathogenic bacteria. The microflora is relatively constant in healthy people, destructing bacteria's beneficial and usual properties [31].

However, this equilibrium could be exaggerated by the nervous tension, leading to disorders as toxins are released by pathogens in the intestine mucosal wall. Thus BLIS is used to keep up a balance of the GIT. The BLIS bacteria avoid the damaging property of inhabitants groups and support

the improvement of the interstitial microflora [32].

Diarrhea

It is complicated to evaluate BLIS's property on diarrhea for several reasons and numerous diarrhea types, but the researchers find out the advantageous property taking place various types of diarrhea. Diarrhea caused by the Rotavirus resulted in deaths globally and is a frequent reason for a problem. The cure for this type of diarrhea, GG has revealed very effectively. The *Lactobacillus reuteri* and *Lactobacillus acidophilus* reported a positive control of diarrhea [33].

Acute diarrhea

Numerous studies have shown that BLIS use is used to treat the acute form of diarrheal infection. The vastness of the research anxious infants, and as a result, the etiology agents were Rotavirus of indefinite reason. Two hundred eighty-seven kids from different countries investigated the intensive trials to check the treatment for acute diarrhea reported. BLIS *S. boulardii* and *Lactobacillus reuteri* showed immensely help for the curement of acute gastrointestinal disorders [34].

Travelers diarrhea

BLIS studied a lot to examine the therapeutic effects of the rate of incidence of diarrhea. Oral intake of *Lactobacillus rhamnosus* terminated the traveler's diarrhea in Turkey, emphasized that GG treats at the rate of 5% of protective and 27.9% in a reading can be seen. Many studies may analyze the BLIS producing bacteria to stop traveler's diarrhea is confirmed; the criteria are related to examination and analysis. The analysis demonstrated the risk between 0.01 was considerably in the period observed that the development of traveler's diarrhea researcher's issue together *Bifidobacterium bifidum* as *buladii* and a combined analysis finished the importance of the therapeutic effectiveness of *Lactobacillus acidophilus* [34].

Treatment for urinary tract infections

Infections of the vagina caused by *Mycoplasma hominis*, *G. vaginalis* and *T.candida* usually microbial agents of girls in the advancement of urinary tract infection which are very frequent and typically urogenital infections are studied every year in healthy girls, BLIS are now being used to treat these infections to some extents [33].

Prevention of dental caries

BLIS has been screened from the mouth cavity this infection could be sensible to evaluate the efficiency for the prevention of dental caries in additional antimicrobial action can be checked [23].

Treatment and hindrance of Cancer by bacteriocin like inhibitory substances

Epidemiological analysis showed that highly use of drenched fats in the food boost the incidents of cancer. Bacteria contain enzyme Nitro-reductase, beta glucosidase azoreductase and carcinogens turns first the dynamic carcinogens in the cologne and might lessen the danger of cancer.

BLIS decreased the bacterial enzyme action even though the specific mode of action is not acknowledged to exploit the tumor [30].

Discussion

Bacteriocin like an inhibitory substance produced in many starter cultures and milk products has the significant potential to improve diverse edible food pieces of stuff. Many authors confirmed that the Nisin produced by many lactic acid bacteria used in many food items to stop *L. monocytogenes*. The data resulting from the antimicrobial substances establish determined that the peptide's existence towards indicator bacteria might be considered BLIS because they have the bacteriocin-like compounds. However, they did not until now been characterized for encoding nucleotide sequences and amino acids [21].

The strain presenting the concern to lipolytic and amylolytic analysis might be considered a substance that originated to class 4th of

bacteriocin-like inhibitory substances (BLIS) [16].

LAB affects pathogenic bacteria's growth due to bacteriocin H₂O₂ and some organic acids that are inhibitory molecules. It is the essential property of BLIS bacteria. For the evaluation, isolates for this parameter as well were used. All bacterial isolates executed varying degrees of inhibitory activity against the indicator pathogenic bacterial strains that include *E.coli*, *Pseudomonas aeruginosa*, and *Listeria monocytogenes* *Staphylococcus aureus*. These isolates showed significant results (P0.05) against *E.coli monocytogenes*, *Staphylococcus* except *Pseudomonas aeruginosa* [15].

The mode of action for inhibitory activity is noticed in various food products, mainly those in which LAB controls the inhabitants due to the development rate's advantage. The natural microflora has now confirmed the inhibitory activity of *L.monocytogenes* in the stationary phase [11].

In recent times the utilization of bacteriocinogenic strains, mainly *Lactobacilli* and *Bifidobacterium*, has been used to equilibrium the gut microbiota and in actuality, their possible defensive ability and therapeutic property have been acknowledged improved the research and industrial interest. The fundamental parameter for evaluating the unique parcels was susceptibility to these bacterial bacteriocin-like inhibitory substances [8].

These bacteriocin producing live bacteria, which have beneficial aspects of human and animal health. Generally, *Lactobacillus* and *Bifidobacteria* were worn BLIS producing bacteria. They should be nonpathogenic and non-toxic. These isolates were susceptible to gastric juice and secreted antibacterial substances. The main benefits of bacteriocin-like inhibitory substances are anti-carcinogenic, anti-hypersensitive, anti-mutagenic, hyper-cholesterolemia, immune-modulatory and anti-osteoporosis [6].

Traditional cheeses encourage the microbiota to participate in dynamic function in attaining food protection through the antimicrobial action of LAB towards spoilage or pathogenic bacteria [3]. The incorporation of bacteriocin-like inhibitory substances is used as a biopreservative component into many food systems and has been proved to help control many pathogenic and spoilage microorganisms. The anti-pathogenic results originated in this reading could give the protection of the microbiota. A most useful and cost-effective choice of introducing bacteriocin-like inhibitory substances into dairy items can be made by adding bacteriocin-producing cultures into food to better the end product's quality and safety [2].

Conclusion

In 21 century, the increasing level of multiple drug resistance towards antibiotics diverts the researcher's attention to inhibit or stop the resistance with alternate antimicrobial agents. Multi-drug resistance of bacteria is developing in many public related health problems in a successful way by developing resistance. To defeat these severe problems, we need innovative methods to control or manage and treat infectious diseases using suitable methods. That may comprise bacteriocin use like inhibitory substances that are safe and secure for better public health, having no side effects. The bacteriocin-like inhibitory substances are nonpathogenic and live microorganisms; when administered in sufficient amounts, they show promising results on their host's physical condition. The selected bacteria are mainly non-spore forming, Gram positive, and lactic acid producing bacteria with bacteriocinogenic characteristics. They are found in rods or cocci shapes and are usually deficient of catalase enzymes while pretending the catalase enzyme can be present in exceptional cases. LAB are ordinary residents of the human GI tract, mainly in the colon, where their amount is 9 logs CFU/g.

The two genera mainly are *Bifidobacterium* and *Lactobacillus*, which are used as the source of bacteriocin-like inhibitory substances. Bacteriocinogenic bacteria, e.g., *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Lactobacillus casei*, are suitable and famous dairy industry their antibiotic benefits.

Bacteriocin-producing microorganisms achieve much importance and undergo an extensive range of research to ensure that they are secure for utilization and possess definite functional bacteriocinogenic properties like antimicrobial action towards pathogens. Many other beneficial bacteriocin effects like inhibitory substances are improving lactose intolerance, increasing utilization of nutrients, lowering serum cholesterol level, and retreating antibiotics. Bacteriocin like inhibitory substances is anti-carcinogenic, anti-hypersensitive, anti-mutagenic, hyper-cholesterolemia, immune-modulatory, and anti-osteoporosis.

The bacteriocin-like inhibitory substances are the option to the therapeutic agents and (GRAS) "Generally Regarded As Safe by the Food & Drug administration economic and readily available in the market.

Authors' contributions

Conceived and designed the experiments: A Qadeer & N Zafar, Performed the experiments: A Ali & R Kanwar, Analyzed the data: S Altaf, M Bilal & S Fatima, Contributed materials/ analysis/ tools: M Gul & GA Ahmed, Wrote the paper: A Ali & N Zafar.

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