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Novel Bioactive Compounds Of Probiotic Bacteria From Milk And Its Various Applications

[1] Vipin Krishna S.L, [2] R.Ragunathan

[1]M.phil Research Scholar, [2]Director & Research supervisor

Centre for Bioscience and Nanoscience Research, Eachanari, Coimbatore - 21, Tamilnadu, India.

ABSTRACT

This paper aims to provide a systematic review of the bioactive compounds produced from probiotic bacteria, role of probiotics and its properties. The use of probiotic bacteria in milk to providing beneficial health effects is today of increasing, interest in the food industry. Milk contains a number of components having functional properties. Milk contains components that provide critical nutritive elements, immunological protection, and biologically active substances for both neonates and adults. Milk proteins are currently the main source of many biologically active peptides. Concentrates of these peptides are potential health-enhancing nutraceuticals for food and pharmaceutical applications.

KEY WORD :

Probiotics, lactic acid bacteria, Bioactive peptides, *Bifidobacterium*, *Lactobacillus*

INTRODUCTION

Microorganisms belonging to the genera of *Lactobacillus, Luconostosc, pediococcus*, and *Bifidobacterium* are the most common probiotics. Most probiotics, which are conveyed through fermented foods and food complements, belong to Bifidobacterium and low GC percentage lactic acid bacteria. The later include *Enterococcus, Lactobacillus, Lactococcus, Leuconostoc, Oenococcus, Pediococcus,* and Streptococcus genera. Species belonging to *Lactobacillus* and *Bifidobacterium* are largely used as probiotics (Felis *et al*.,2007).

Many lactic acid bacteria species play a major role in the ripening process of cheese, especially to improve the consistency, aroma, and flavor of the milk products (Hannon *et al*., 2003). Certain lactic acid bacterial strains are characterized by their ability to transform lactose and improve the digestibility of fermented dairy products (Weinberg *et al*., 2007) as well as their preservation (Abdelbasset and Djamila., 2008). They are also employed for improvement of the texture, taste, and viscosity in the manufacture of dairy products

(Soukoulis *et al*., 2007). Lactic acid bacteria can be recovered from fermented foods and beverages, vegetables, milk, and dairy products.

Lactic Acid Bacteria are a group of Gram-positive, non-sporulating, anaerobic, or facultative aerobic cocci or rods, which produce lactic acid as one of the main fermentation products of the metabolism of carbohydrates (Katla and Axelsson *et al*., 2000). These bacterias are the major components of the starters used in fermentation, especially for dairy products, and some of them are also natural components of the gastrointestinal microflora. *Lactobacillus* is one of the most important genera of lactic acid bacteria (Coeuret and Bernardeau *et al*. (2003). These organisms produce various known compounds such as bacteriocin which can antagonize the growth of some pathogenic bacteria in foods (Abdelbasset, Djamila., 2008). Lactic acid bacteria are regarded as a major group of probiotic bacteria and have been used successfully to treat acute infantile diarrhoea and various types of illnesses (Buie and Gorbach, *et al*., 1995). Various types of microorganisms including yeasts, molds, and bacteria are present in raw milk. Among these organisms, only the (LAB) lactic acid bacteria have the property of producing lactic acid from milk sugars by the process of fermentation and thus lactic acid bacteria constitute the predominant organism in the milk (Delacroix-Buchet., 2002). These lactic acid bacteria are called probiotics and, it is defined classically as a viable microbial dietary supplement that beneficially affects the host through its effects in the intestinal tract. Probiotics are viable lactic acid microorganisms that are helping to provide health benefits when administered in appropriate quantities. The lactic acid bacteria can produce antibacterial substances including bacteriocins which inhibit the growth of several pathogenic bacterias. (Corthier.,2011).

Probiotics, microorganisms that are useful to health when consumed. Milk and milk products are usually associated with probiotic bacteria, which provide supplements for the beneficial maintenance of the intestinal system (Tambekar and Bhutada *et al.*, 2010). The prime Lactic acid-producing bacterial (LAB) groups are gram-positive, catalase-negative organisms and they belong to genera *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, and *Leuconostoc* (Leroy and De Vuyst., 2004). There has been increasing attention to the use of diverse strains of lactic acid bacteria as probiotics, mainly *Lactobacilli* and *Bifidobacteria* that are residents of the commensal bacteria in the gut of humans showing good therapeutic functions (Lavanya *et al*., 2011). They can produce antimicrobial substances such as organic acid, hydrogen peroxide, and bacteriocins, which can influence the growth of possible harmful microorganisms.

Milk contain wide variety of proteins that provide protection towards enteropathogens or are crucial for the manufacture and characteristic nature of certain milk products (Korhonen and Pihlanto., 2004). Milk has been shown to contain wide varities of bioactive compounds, which extend the range of influence of mothers over young beyond nutrition (Gobbetti *et al*. 2007). Peptides are in a latent or inactive state within protein molecules however can be released all through enzymatic digestion. Biologically active peptides released from caseins and whey proteins include 3 to 20 amino acids per molecule (Korhonen and Pihlanto ., 2004). Researchers for the last decade have verified that these bioactive peptides possess very vital biological functionalities, which include antimicrobial, antihypertensive, antioxidative, anticytotoxic, immunomodulatory, opioid, and mineral-carrying activities.

Most of the bioactivities of milk proteins are latent, being absent, or incomplete in the original native protein, however full activities are manifested upon proteolytic digestion to release and activate encrypted bioactive peptides from the original protein (Clare and Swaisgood 2000; Gobbetti *et al.*, 2002). Bioactive peptides (BPs) have been identified inside the amino acid sequences of native milk proteins. They may be released by using proteolysis during gastrointestinal transit or food processing. Enzymes such as digestive, naturally taking place in milk, coagulants, and microbial enzymes, particularly these from adventitious or lactic acid starter bacteria, commonly generate these bioactive compounds. BPs are released from milk proteins during milk fermentation and cheese maturation, which enriches the dairy products (Gobbetti et al., 2002).

Characteristics of Probiotics

In different research studies, probiotics have special viable properties

- Probiotics wanted to have excessive cell viability.
- It has to be capable to adequate the interaction or send signaling activity of immune modulator.
- It must have the ability to influence local metabolic activity.
- It ought to be healthy for surviving and processing in the intestine condition like resistance to low pH and organic acids.
- Probiotics should be stable, safe, effective and equipped for staying viable for periods under storage and field conditions.
- It must have strength of repair and substitute the intestinal micro flora.
- It has to have anti-carcinogenic and anti-mutagenic activity, cholesterol reducing effects, can keep mucosal integrity and can enhance bowel motility (Divya, 2016).
- It must be able to speed up, facilitate and colonize/maintain the digestive tract.
- They need to have the capacity to withstand gastric juices and the exposure to bile acid which looks to be essential for oral administration.
- Adhesion to mucosal and epithelial surfaces, an vital property for successful immune modulation, aggressive exclusion of pathogens, as properly as prevention of pathogen adhesion and colonization.

Health Benefits of Probiotics

Probiotic remedy has attracted research interest in human infectious, inflammatory, and allergic diseases. The confined proof gained thus far indicates that the introduction of cultures of really useful microorganisms of the healthful human microbiota holds outstanding promise for the treatment of scientific conditions related to impaired intestine mucosal barrier features and sustained inflammatory responses. The future focus of probiotic research must concentrate on scientifically documented outcomes of clearly defined strains. Probiotic modulation of intestinal microbiota targets at reduction of the threat of gut-associated diseases .(Isolauri *et al*, 2004).

There is increasing evidence in favour of the claims of beneficial consequences attributed to probiotics, which includes enchancment of intestinal health, enhancement of the immune response, reduction of serum cholesterol, and most cancers prevention. These health properties are strain specific and are impacted via a number mechanisms stated above. While some of the health benefits are properly documented others require additional research in order to be established. In fact, there is sizeable proof to assist probiotic use in the treatment of acute diarrhoeal diseases, prevention of antibiotic-associated diarrhoea, and enchancment of lactose metabolism, however there is inadequate proof to suggest them for use in different clinical conditions. Kechagia *et al*., (2013).

A lactic acid bacterium has been shown to increase folic acid content material of yogurt, buttermilk and kefir and to extend niacin and riboflavin levels in yogurt, vitamin B12 and vitamin B6 in cheese. LeBlanc *et al*., (2007). In addition to nutrient synthesis, probiotics may additionally enhance the digestibility of some dietary nutrients such as protein and fat.(Panesar *et al*., 2009). Probiotics can be combined with enzymes that help to break down food components into simpler compounds to enhance nutrient digestion.Short-chain fatty acids such as lactic acid, propionic acid and butyric acid produced through lactic acid bacteria can also help keep an appropriate pH and protect towards pathological modifications in the colonic mucosa. Synthesized nutrients which include folic acid, niacin, riboflavin, vitamins B6 & B12 can amplify nutrient bioavailability. (Singh *et al*., 2011).

Lactic acid bacteria as a probiotic

LAB represents a ubiquitous and heterogeneous species with the common characteristic of lactic acid production. Taxonomically, LAB species are found in two distinct phyla, particularly Firmicutes and Actinobacteria. Within the Firmicutes phylum, LAB belongs to the *Lactobacillales* order and consists of the following genera: *Lactobacillus, Lactococcus, Leuconostoc, Oenococcus, Pediococcus, Streptococcus, Enterococcus, Tetragenococcus, Aerococcus, Carnobacterium, Weissella, Alloiococcus, Symbiobacterium,* and *Vagococcus* which are all low guanine-cytosine (GC) content material organisms (Kockova *et al*., 2011, Pfeiler & Klaenhammer, 2017 & Axelsson., 1998).

lactic acid bacteria (LAB) are extensively used in several industrial applications, ranging from starter cultures in the fermented food industry to probiotics in dietary supplements, and as bioconversion agents. Due to the confined biosynthetic skills and their excessive necessities in terms of carbon and nitrogen sources, the natural habitat of lactic acid bacteria is represented by using nutritionally rich environments. LAB is normally associated with plant and animal raw materials, and the corresponding fermented food products, such as dairy, meat, vegetable, and cereal plant environments, the place fermentation can occur. Some species also take place in the respiratory, intestinal, and genital tracts of human beings and animals. The capability to colonize such a range of habitats is a direct consequence of the broad metabolic versatility of this team of microorganisms. (Wedajo., 2015).

Sources of bioactive protein

Milk

Milk contains two major protein groups, caseins and whey proteins, which differ greatly with regard to their physicochemical and biological properties. Casein, which makes up 80% of the total protein in milk, is found primarily in large complexes called micelles (Svaisgood, H. E. 1992).The multiple functional properties of caseinate derivatives allow them to be used in several food products, e.g. bakery and meat products, soups and toppings (Mulvihill, D. M. 1992) The caseins are known to exhibit biological activity, such as carrying of calcium, zinc, copper, iron and phosphate ions in the body (Table 1). In addition, casein functions as a precursor for many different bioactive peptides (Mulvihill, D. M. and Fox, P. F. 1994)'

Transgenic milk proteins

Transgenic animals have been employed as in vivo experimental models for assessing the ability and impact of foreign gene expression in a biological system. Although transgenic mice are the most commonly used, transgenic sheep, goats, pigs, and cows have also been developed for specific applications. Transgenic techniques have been applied to these animals with the aim of altering the properties of milk by adding new proteins or recovering proteins for other uses such as pharmaceuticals (Wall, R. J., Kerr, D. E. and Bondioli, K. R. 1997).

Other sources

In addition to milk and eggs, the bioactive protein is found in many other biological materials. Among these are animal proteins such as gelatin and fish muscle protein, and plant proteins suchas corn α -zein ,rice glutelin, prolamin, wheat gluten, and soy protein (Ariyoshi, Y. 1993).

protein	concentration g/l	function
Caseins (α,β and k)	28	Ion carrier (Ca, PO4, Fe, Zn, Cu), precursors of bioactive peptides
β -lactoglobulin	1.3	Retinol carrier, fatty acids binding, possible antioxidant
α -Lactalbumin	1.2	Lactose synthesis in mammary gland, Ca carrier, immunomodulation, anticarcinogenic
Immunoglobulins A, M and G	0.7	Immune protection
Glycomacropeptide	1.2	Antiviral, bifidogenic
Lactoferrin (LF)	0.1	Antimicrobial, antioxidative, immunomodulation, iron absorption, anticarcinogenic
Lactoperoxidase	0.03	Antimicrobial
Lysozyme	0.0004	Antimicrobial, synergistic effect with immunoglobulins and LF

Table 1. Biological activity of major milk proteins, (Korhonen, H. 1995)

Mechanism of Probiotic action

The effects of probiotics can be categorised into three modes of action. The first is related to the modulation of the host's defenses which is most possibly essential for the prevention and treatment of infectious disease and additionally for therapy of intestinal inflammation. Probiotics might also impact the immune system by means of products such as metabolites, cell wall elements, or DNA. These products can be identified by means of the host cells sensitive for these due to the fact of presence of a specific receptor. (Cummings *et al*., 2004). The fundamental target cells are typically the intestine epithelial and gut-associated immune cells. Finally, the interaction between probiotics and the host's immune cells by using adhesion would possibly be the triggering signaling cascade main to immune modulation .(Corthésy, Gaskins & Mercenier., 2007).

Mechanisms of action of probiotics as highlighted, have additionally generalized the mechanisms of probiotics which can be summarized as follows:

Probiotics compete in opposition to pathogenic bacteria to bind to intestinal epithelial cells, Probiotics enhance the intestinal epithelial barrier characteristic by way of increasing mucin production, preventing pathogens from inflicting damage to the epithelium, and lowering cell permeability. In addition, probiotics additionally enhance the mucosal barrier feature with the aid of inducing the expression of antimicrobial peptides such as defensins, they inhibit pathogenic growth via the secretion of antimicrobial peptides such as bacteriocins and reuterin. For example, lactic acid bacteria inhibit pathogen growth by growing an acidic environment thru the manufacturing of organic acids, probiotics additionally stimulate the manufacturing of serum Immunoglobin A (IgA) and secrete IgA which plays an important function in intestinal humoral immunity, they decorate phagocytosis, amplify the activity of natural killer cells, promote cell-mediated immunity, and stimulate quite a number of different non-specific immune responses in opposition to pathogens. probiotics down-regulate pro-inflammatory cytokine production, stop apoptosis and suppress the proliferation of T cells for this reason stopping more than a few inflammatory conditions. they produce hydrogen peroxide which suppresses pathogens related to bacterial vaginosis .Bermudez-Brito., (2012).

The probiotic organisms should be a natural inhabitant in the host and must have the ability to survive in an environment where they are administered giving beneficial effects to the host. Additionally, a potential probiotic strain should also be able to adhere to the mucosal surface and successfully colonize the gastrointestinal tract. This is because long-term adherence has been associated with greater probiotic potentiality as it enhances the immune system by inducing a local immune response and antigen assimilation. Most species from the genera *Lactobacillus* and *Bifidobacterium*, and some from *Lactococcus, Enterococcus, Streptococcus,* and *Saccharomyces* exhibit above- mentioned properties and are hence mostly selected for probiotics. (Renita jobby *et al*.,2020).

In *Lactobacillus acidophilus,* it is mostly recognized to have probiotic effects and is one of the most commonly suggested organisms for dietary use (Shah., 2007). It is frequently added to yogurt and fermented milk products, with 80% of the yogurts produced in the United States containing *L. acidophilus* (Sanders, 2003). *L.acidophilus* isolates also form part of the natural human microflora and have been cultured from the oral (Ahrn *et al*., 1998), and vaginal (Rogosa & Sharpe., 1960) tracts, digestive (Kulp & Rettger., 1924). Here, the key research on *L. acidophilus*, spanning its original isolation as normal human microbiota and describing its genomic, biosynthetic, and probiotic characteristics. In addition to emphasizing a need for rigor in describing *L. acidophilus* isolates by highlighting recent studies that incorrectly report the identity of isolates.

Secondary metabolites ,which can be defined as extracellularly released peptides or proteins. Molecules that have low molecular weight with a bacteriostatic mode of action closely related species. Bacteriocins are classified into three, based on their structure and function (Klaenhammer *et al*., 1993). There are several bacteriocins produced by probiotics in the form of a purified or concentrated compound that can be used as a bio preservative to control undesirable bacteria remains a primary focus of research to food safety and quality of the product (Schillinger *et al*., 1996).

Most of the Lactic acid bacteria(LAB) may show antagonistic activity against certain different types of pathogenic bacteria(Byun., 1997) Consumption of huge amount of milk, fermented dairy products with a wild Lactobacillus strains and Bifidobacteria showed reduction in serum cholesterol level in human (Mann ., 1974).

Antimicrobial activity, bile salts, and acid tolerance are three important features for screening probiotic potential of bacteria that can be used as medical. LAB produce organic acids, hydrogen peroxide, diacetyl, bacteriocins, and antifungal compounds such as fatty acids during lactic fermentation. Bacteriocins are protein compounds with growth inhibition ability of sensitive pathogenic bacteria and different degradation system in digestive system compared with antibiotics. LAB are resistant to lysozyme, gastric acid, gastrointestinal juice, and bile salts. Antimicrobial compounds are also prepared from them to compete and inhibit pathogenic microorganisms. Such compounds may affect metabolism or toxins of pathogenic bacteria.

Acid Bile Tolerance

The first criteria for probiotic strains are their tolerance to acid and bile. Bacteria used as probiotic strains are joined in the food system with a journey to the lower intestinal tract via the mouth. In this food system, probiotic bacteria should be resistant to the enzymes like lysozyme in the oral cavity. It goes to the stomach and enters the upper intestinal tract which contain bile. The stains should have the ability to resist the digestion process. The viability and activity of probiotics are needed at the lower digestive tract, these organisms should withstand the adverse conditions encountered in the host's upper gastrointestinal tract (Ding and Shah,2008). Strains need to be resistant to the stressful conditions of the stomach (pH 1.5-3.0) and upper intestine which contain bile (Chou and Weimer, 1999). To show probiotic property, they should reach to the lower intestinal tract and maintain themselves there. Bile acids are synthesized in the liver from cholesterol and sent to the gallbladder and secreted into the duodenum in the conjugated form (500-700 ml/day). In the large intestine these acids suffer some chemical modifications (deconjugation, dehydroxylation, dehydrogenation and deglucuronidation) due to the microbial activity. Conjugated and

deconjugated bile acids show antimicrobial activity especially on Escherichia coli subspecies, Klebsiella spp., and Enterococcus spp. The deconjugated acid forms are more effective on gram positive bacteria (Dunne et al., 2001).

Antimicrobial activity

Antimicrobial activity is one of the most important selection criteria for probiotics. Antimicrobial activity tartest the enteric undesirables and pathogens (Klaenhammer Kullen,1999). Antimicrobial effect of lactic acid bacteria are formed by producing some substances such as organic acid (lactic, acetic, propionic acid), carbon dioxide, hydrogen peroxide, diacetyl, low molecular weight antimicrobial substances and bacteriocins (Quwehand and Vesterlund, 2004 and Cakir, 2003). Saranya & Hemashenpagam (2011) mentioned that the LAB inhibited all the pathogenic bacteria. The activity of LAB on some gram positive and negative pathogenic bacteria such as E. coli, Pseudomonas aeroginosa, Klebsiella pneumonia, Staphylococcus aureus and Bacillus 19 cereus and the inhibition zones were in the range of 1.4 to 2.8 cm. The largest zone of inhibition was produced by Lactobacillus. plantarum against Staphylococcus. aureus. In the present study also Lactobacillus sp. (PPTG 1) is also possessing antibacterial activity, especially on Staphylococcus aureus with up to 19 mm Staphylococcus aureus with 19 mm, average zone of inhibition against Escherichia coli with 12 mm, minimum inhibition against Bacillus cereus with 11 mm.

Anti-diarrhoeal effect

(Jones.2010) found probiotic consumption to be useful in the treatment of many types of diarrhoea, including antibiotic-associated diarrhoea in adults, travellers' diarrhoea, and diarrheal diseases in young children caused by rotaviruses. The most commonly studied probiotic species in these studies have been Lactobacillus GG, Lactobacillus casei, Bifidobacterium bifidum and S. thermophilus. Because diarrhoea is a major cause of infant death worldwide and can be incapacitating in adults, the widespread use of probiotics could be an important, non-invasive means to prevent and treat these diseases, particularly in developing countries.

CONCLUSION

This review considers an overview of the role of probiotic bacterias, the bioactive compounds, antioxidant activity, antimicrobial activity Acid Bile Tolerance, Anti-diarrhoeal effect of milk. In future, identifcation of new variants and consumption of newly formulated probiotics may be a good strategy for promoting future health. Therefore, probiotics can be recommended as an alternative biotherapy for treating various infections.

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