Microbes and Infectious Diseases

Mini-review article

Antimycobacterial, anticancer, and antiviral properties of probiotics: An overview

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A R T I C L E   I N F O

A B S T R A C T

Probiotics are live microorganisms that when administered in sufficient amounts, confer a health benefit to the host. Bacteria are the dominant group of microbes in the naturally fermented foods. Major genera of probiotics associated with fermented foods are *Lactobacillus* spp., *Lactococcus* spp., *Leuconostoc* spp., *Macrococcus* spp., *Pediococcus* spp., *Bacillus* spp., and *Bifidobacterium* spp. Currently, the beneficial aspects of probiotics on human health and nutrition are constantly increasing. Probiotic bacteria are known to exhibit potential activities against infectious diseases causing pathogens, particularly various species of *Mycobacterium*. Probiotics are considered to prevent tumor growth by maintaining homeostasis mechanisms. Substantial research activities showed that probiotics had antiproliferative or pro-apoptotic activities against various human cancer cells. In addition, probiotics have exhibited their potential role as antiviral agents against several groups of viruses. This review overviews the antimycobacterial, anticancer, and antiviral traits of probiotics isolated from different sources for its pivotal therapeutic applications in the future.

Introduction

Research on fermented foods and its global productivity had escalated rapidly in the 21st century. Over the past few years, the demands of functional foods have increased tremendously again due to their medicinal values [1]. Naturally fermented foods have nutritive as well as non-nutritive constituents, which have the potentiality to modulate specific target functions relevant to human health [2]. In view of the techno-functional significance, traditional fermented foods occupy an important place in the diet of people. Vegetables, bamboo shoots, fish, meat, beans, milk, cereals, and millets are the most common substrates used for the preparation of fermented foods [3].

Traditionally prepared fermented foods are generally considered to contain heterogeneous groups of probiotics [4]. Probiotics are live fed microorganisms that when administered in adequate amounts, confer a health benefit to the host such as stimulation of immunity, reduction of serum cholesterol content, growth inhibition of pathogens, etc. [5]. Probiotics are also known to depict anti-allergic, tumoricidal, anti-*Helicobacter*, and anti-inflammatory properties [6]. The potential probiotics must exhibit resistance to acidic conditions, tolerance to bile, and ability to colonize the gastrointestinal tract [7,8]. Currently, the beneficial aspects of probiotics on human health and nutrition are constantly increasing [9]. Fermented foods are important consortia for diversified categories of probiotics bacteria as leading microflora. Bacteria are

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dominant in both the naturally fermented foods and foods fermented by the supplementation of starter cultures. Among the distinct bacterial cultures, lactic acid bacteria (LAB) are commonly involved in providing acidity to the fermented foods, while non-LAB are involved in the fermentation of foods, frequently as minor or secondary groups [10].

Antimycobacterial activity of probiotics

Mycobacterium tuberculosis (*M. tuberculosis)* is the causative agent of tuberculosis (TB). The intracellular pathogen, *M. tuberculosis* primarily infects human pulmonary macrophage [11]. Macrophages are specialized cells of the immune system that engulf and remove the invading microorganisms through the phagocytosis process [12]. In general, during this process, microorganisms other than *M. tuberculosis* are trapped into the phagosomes which fuse with lysosome and forms phagolysosome. Eventually, the digestive process occurring inside the phagolysosomes destroys invaded microorganisms. However, *M. tuberculosis* after phagocytised escapes from this defence mechanism by infecting macrophages and survive within the adverse environment [13]. *Mycobacterium tuberculosis* utilizes macrophages for its own replication process. The defensive property of *M. tuberculosis* relies on several survival strategies. Unlike non-pathogenic mycobacterium strains, first of all, the pathogenic *M. tuberculosis* arrests the maturation process of phagosomes and prevents the acidification of phagosomal compartments. It also inhibits the formation of the lysosomes and phagosomes complex. Further, the bacterium impairs the apoptosis of macrophage and suppresses the antimicrobial responses, thus helping the bacterium to escape from the phagosomes [14]. The bacterium becomes undetectable to the innate immune system because major histocompatibility complex class II antigen avoids its presentation. In this manner, *M. tuberculosis* can manipulate and survive in the adverse environment of pulmonary or any other parts of the host macrophages [15]. Extensive reports have demonstrated that in spite of the digestive property of macrophages, *M. tuberculosis* has developed multiple adaptive strategies to destruct the phagosomal pathways and survive intracellularly in the host macrophages [16]. The cell envelope of *M. tuberculosis* constituting diverse lipid contents is a major factor in its virulence property [13].

Despite the discovery of first-line and second-line anti-TB drugs, TB continued to ravage at global scale. In the current scenario, there is an emergence of multi-drug resistant (MDR) strains, threatening global TB control. Multi-drug resistant TB is a form of TB that is resistant to first-line anti-TB drugs, at least to isoniazid and rifampicin. The rise of MDR-TB led to the use of second-line drugs (para-aminosalicylic acid, cycloserine, terizidone, ethionamide, prothionamide, thioacetazone, linezolid, levofloxacin, moxifloxacin, ofloxacin, gatifloxacin, and capreomycin) that are very expensive and require long term treatment [13]. On the other hand, Bacillus Calmette-Guérin (BCG) vaccine has shown pivotal efficacy in combating TB. But the lack of protecting pulmonary infections is the poor aftermath of this preventive approach [14]. In this regard, the identification of new potential anti-tubercular agents or vaccines is the desperate demand of this hour.

Probiotic bacteria associated bacteriocins have exhibited potential activities against various species of *Mycobacterium*. Nisin (a bacteriocin) was assessed against *Mycobacterium smegmatis* and revealed 97.7±2% of reduction in internal ATP and leakage of intracellular ATP [17]. **Mota-Meira et al.** [18] revealed antimycobacterial activities of nisin A and mutacin B-Ny266 (type A lantibiotics) against *M. smegmatis*. The study of **Donaghy et al.** [19] demonstrated that the cell-free supernatant of cheese associated *Lactobacillus paracasei* inhibited the growth of *Mycobacterium avium* subsp. *paratuberculosis*. Bacteriocin of probiotic bacteria isolated from *Boza* (Turkish beverage) showed antimycobacterial activity. *L. plantarum* ST194BZ associated bacteriocin depicted anti-tubercular activity against *M. tuberculosis* with 69% of reduction in bacterial growth, whereas, *L. paracasei* ST242BZ, *L. plantarum* ST414BZ, and *L. plantarum* ST664BZ exhibited 50% inhibition of bacterial growth. In another report, bacteriocins from *L. plantarum* ST202Ch, *L. plantarum* ST216Ch, *L. sakei* ST153Ch, *L. sakei* ST154Ch, and *Enterococcus faecium* ST211Ch (isolated from Portuguese fermented meat products) showed anti-tubercular activities by reducing the growth of *M. tuberculosis* from 16.1 to 48.6% [20]. **Sosunov et al.** [21] demonstrated that *L. salivarius*, *Streptococcus cricetus*, and *E. faecalis* associated bacteriocins had promising dose-dependent antimycobacterial activities comparing to rifampicin. **Carroll et al.** [22] depicted the antimycobacterial activities of lacticin 3147 against *M. kansasii* and *M. tuberculosis* H37Ra. Lantibiotics certainly reveal potentiality for future TB treatment. Another study showed that nisin and lacticin 3147 arrested the bacterial lipid II moiety and

suggested that inherent cell wall alterations did not provide lantibiotic resistance to mycobacteria [23]. Bacteriocins purified from *Pediococcus pentosaceus* VJ13 exhibited antimycobacterial activity against *M. smegmatis*. **Zahir et al.** [24] demonstrated that the proteinaceous inhibitory substances produced by *Aerococcus* sp. ZI1 had antimycobacterial properties against *M. smegmatis*. **Mariam** [25] depicted the antagonistic characteristics of lactobacilli starter cultures against *M. bovis*. **Sosunov et al.** [21] purified 5 varied kinds of bacteriocins with antimycobacterial traits which were tested further using various models including *in vitro Mycobacterium* cultures, *in vitro* infection of mouse macrophages, and *in vivo* infection of inbred mice. Likewise, *L. plantarum* and its bacteriocin (plantaricin 42) were encapsulated in nano-fibers. The findings suggested that this technique may be incorporated for the potential delivery of antimycobacterial bacteriocins to the specific sites of infections [26]. Recently, coagulase-negative staphylococci isolated from fermented foods have been investigated as probiotics [27-29] and showed a pivotal role as anti-tubercular agents [30-32]. In addition, peptides isolated from coagulase-negative staphylococci also showed potential anti-tubercular role [33-35].

Probiotics show anti-mycobacterial properties through various modes of action, particularly by inhibiting the synthesis of cell wall as well as creating pores in the bacterial cell membrane by binding to the peptidoglycan precursor, reducing the constituents of proton motive force in mycobacterium, and targeting ATP-dependent protease of bacterium [13].

Anticancer activity of probiotics

Cancer is a multi-cellular and multi-genic non-infectious disease that is the colossal public burden globally [36]. According to the recent Global Cancer Statistics, there are approximately 32.6 million cancer patients worldwide, representing it as one of the primary causes of mortality in the world [37]. Cancer cells show high rate of proliferation due to self-sufficient growth signals and sustained angiogenesis. Further, these cells invade tissues, show metastasis, and reveal resistance towards apoptosis [38].

Specific mechanism associated with anticancer traits of probiotics remains unclear. However, probiotics are considered to prevent tumor growth by maintaining homeostasis mechanisms. Another cancer-preventing strategy involving probiotic bacterium is linked to the binding and degradation of carcinogens. Unhealthy foods contain several mutagenic compounds which are associated with the increased risk of colon cancer. Ingestion of probiotics alleviated the mutagenic effect of diet rich in cooked meat, which resulted in a reduced urinary and fecal excretion of heterocyclic aromatic amines. Supplementation with dietary probiotics have shown to down-regulate the uptake of 3-amino-1-methyl-5H-pyrido (4,3-β) indole (Trp-P-2) and its metabolites [39]. Probiotics can be a potential candidate for oral cancer therapy by increasing mRNA expression of phosphatase and tensin homolog (PTEN) and down regulation of mRNA expression and Mitogen-Activated Protein Kinases (MAPK). The probiotics mixture VSL#3 suppresses the Cyclooxygenase-2 (COX2) expression in Colo320 and SW480 intestinal epithelial cells [40].

Substantial research activities showed that probiotics had antiproliferative or proapoptotic characteristics against diverse human cancer cells. **Lee et al.** [41] reported significant anticancer traits of *L. acidophilus*, *L. casei*, and *B. longum* against few cell lines. Previous findings exhibited the antiproliferative traits of the cytoplasmic extracts from *L. rhamnosus* strain GG in human gastric as well as colonic cancer cells [42-44]. *B. adolescentis* SPM0212 showed the inhibition of the proliferation of colon cancer cell lines viz. HT-29, SW 480, and Caco-2 [45]. Probiotics such as *B. polyfermenticus* [46], *L. acidophilus* 606 [47], LGG/Bb12 [48], and LGG/*B. animalis* subsp. *lactis* [49] revealed anticancer activities against colon cancer cells. **Cousin et al.** [50] demonstrated that *Propionibacterium freudenreichii* had the potentiality to improve the cytotoxicity of camptothecin that was implied as a chemotherapeutic agent for gastric cancer. In another *in vitro* study, the anticancer activities of probiotics were demonstrated against colorectal carcinoma cells [51]. Other examined cell types also included cervical cancer cells [52], breast cancer cells [53], and myeloid leukemia cells [54].

According to **Chiu et al.** [55], *L. casei* and *L. rhamnosus* have properties to induce the apoptosis of the human monocytic leukemia cell line. In another study, **Choi et al.** [56] demonstrated the anticancer impact of *Lactobacillus* spp. on various human cancer cell lines. Peptidoglycans of the cell walls of varied probiotic bacteria, particularly lactobacilli exhibited anticancer traits [57]. **Wang et al.** [58] evaluated *in vitro* anticancer activities of *L. plantarum* derived exopolysaccharide against HepG-

2, BGC-823, and HT-29 cell lines. Results suggested that the EPS produced by *L. plantarum* might be an alternative for natural anticancer drugs. **Knecht et al.** [59] reported antiproliferative properties of the cell-free filtrate and the cell-free lyophilized filtrate of *Pediococcus pentosaceus*, *L. plantarum*, and *Weissella confusa* on colorectal adenocarcinoma cells. **Lee et al.** [60] reported anticancer traits of *Lactococcus lactis* KC24 against gastric carcinoma (AGS), colon carcinoma (HT-29 and LoVo), breast carcinoma (MCF-7), and lung carcinoma (SK-MES-1) cells.

L. lactis KC24 showed anticancer activities against various cancer cell lines such as lung carcinoma (SK-MES-1), breast carcinoma (AGS and MCF-7), and colon carcinoma (HT-29 and LoVo) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [61]. Another study demonstrated the anticancer and anti-inflammatory activities of *L. lactis* NK34 against various cancer cell lines like DLD-1 (human colon adenocarcinoma cell line), SK-MES-1 (human lung carcinoma cell line), LoVo (human colon adenocarcinoma cell line), HT-29 (human colon adenocarcinoma cell line), AGS (human stomach adenocarcinoma cell line), and MCF-7 (human breast adenocarcinoma cell line). The cytotoxicity of NK34 strain was reported against normal and cancerous cells using MTT assay. In addition, the anti-inflammatory trait of *L. lactis* NK34 exerted a reduction in pro-inflammatory cytokines [62].

Rajoka et al. [63] demonstrated *in vitro* anticancer activity of *L. kefiri* MSR101 associated EPS against HT-29 cell lines. Results suggested that MSR101 derived EPS had not only potential anticancer trait on HT-29 cancer cells but also up-regulated the expression of Cyto-c, BAX, BAD, caspase3, caspase8, and caspase9. In general, results suggested that the EPS from *L. kefiri* MSR101 may not only be used as a functional food product but also considered as a topical medication due to their effectiveness against colon cancer.

Awaisheh et al. [64] screened the anticancer traits of cell extracts of 40 potential probiotic bacteria against 2 colorectal cancer cell lines (Caco-2 and HRT-18), and Vero cells using MTT and Trypan Blue assays. Results demonstrated that *L. acidophilus* LA102 and *L. casei* LC232 had promising cytotoxic properties with anti-proliferation characteristics of 37 and 68.5% for LA102, and 48 and 45.7% for LC232 against Caco-2 and HRT-18, respectively.

The anticancer activities of *L. acidophilus* 36YL were tested against 4 human cancer cell lines (AGS, HeLa, MCF-7, and HT-29) and one normal cell line (HUVEC) using cytotoxicity assay and apoptosis analyses. Results showed satisfactory anticancer activities against 4 tested cancer cell lines and exerted negligible side effects on the normal cell line. Findings revealed that the anticancer characteristics of *L. acidophilus* 36YL strain secretions rely on the induced apoptosis in cancer cells. *L. acidophilus* 36YL strain is considered as a nutraceutical alternative or a topical medication with a potent therapeutic index due to the lack of cytotoxicity towards normal cells but significant toxicity to cancer cells [65].

Antiviral properties

The virus is a submicroscopic infectious agent that replicates only inside the living cells of an organism and infects both humans and animals. Most viruses have either RNA or DNA as their genetic material. The nucleic acid may be single- or double-stranded. Viruses are causative agents of several deadly diseases including Zika virus disease, Ebola virus disease, Influenza virus disease, Herpes simplex virus (HSV) disease, Hendra virus disease, and coronavirus disease [66-68].

Hand, foot, and mouth disease (HFMD) pandemics are a threat to public health. The antiviral activity of two commercially available probiotics, namely *L. reuteri* Protectis and *L. casei* Shirota, was demonstrated against Coxsackieviruses and Enterovirus 71 (EV71), the key agents responsible for HFMD. *In vitro* infection set-ups using human skeletal muscle and colon cell lines were designed to evaluate the antiviral effect of the probiotic bacteria during entry and post-entry steps of the infection cycle. Findings indicated that *L. reuteri* Protectis displayed a significant dose-dependent antiviral activity against Coxsackievirus type A (CA) strain 6 (CA6), CA16, and EV71, but not against Coxsackievirus type B strain 2. Data supported that the antiviral effect is likely achieved through direct physical interaction between bacteria and virus particles, which impairs virus entry into its mammalian host cell. No significant antiviral activity was estimated with *L. casei* Shirota. The study showed the potential to address the urgent need for a safe and effective means to protect against HFMD and limit its transmission among children [69].

The activity of probiotic strain *B. subtilis* 3 against the influenza virus was determined. The

antiviral property of strain was demonstrated *in vitro* and *in vivo*. A new peptide, P18, produced by the probiotic strain was used for antiviral activity. Cytotoxicity studies demonstrated no toxic effect of P18 on Madin-Darby canine kidney (MDCK) cells, even at the highest concentration tested. Complete inhibition of the influenza virus *in vitro* was observed at low concentrations. The protective effect of P18 in mice was comparable to that of oseltamivir phosphate (Tamiflu). The study revealed the potential of peptide P18 as an antiviral compound for the development of new antiviral vaccines [70].

Transmissible Gastroenteritis Virus (TGEV) is the highly contagious causative agent of the enteric and respiratory pathology and diarrhoea, vomit, and dehydration clinical symptoms which ends up with death of newborn piglets. Authors evaluated the protective impact of *L. plantarum* strain N4(Lp) which metabolic products were added to the swine testis (ST) cells with three different orders using MTT cell proliferation assay and CPE analysis. Metabolic products led to the dose-dependent rescue of the viability of infected cells in a certain order: pre-treatment, post-infection, co-incubation. Pre-treatment of cells with probiotic metabolic products reduced viral proliferation up to 78% at non-cytotoxic concentration 1/4 dilution. The viral yields in pre-treatment groups were reduced by over three log10 units [71].

The antiviral potential of four probiotic metabolites (*Lactobacillus* and *Bifidobacetrium* species) was determined against rotavirus *in vitro* infection monitored by the NSP4 protein production and Ca^{2+} release. Significant results were obtained with the metabolites of *L. casei*, and *Bifidobacterium adolescentis* in the reduction of the protein production and Ca^{2+} liberation in the intracellular model, which suggests a successful antiviral activity against RV infection. Findings demonstrated that probiotic metabolites were able to interfere with the final amount of intracellular NSP4 protein and a successful Ca^{2+} regulation, which suggested a new approach to the mechanism exerted by probiotics against the rotavirus infection [72]

L. plantarum DK119 (DK119) isolated from the fermented Korean cabbage food was used as a probiotic to determine its antiviral effects on the influenza virus. DK119 intranasal or oral administration conferred 100% protection against subsequent lethal infection with influenza A viruses, prevented significant weight loss, and lowered lung viral loads in a mouse model. The antiviral protective

efficacy was observed in a dose and route dependent manner of DK119 administration. Mice that were treated with DK119 showed high levels of cytokines IL-12 and IFN-c in bronchoalveolar lavage fluids, and a low degree of inflammation upon infection with influenza virus. Depletion of alveolar macrophage cells in the lungs and bronchoalveolar lavages completely abrogated the DK119-mediated protection. Findings indicated that DK119 can be used as an ideal antiviral probiotic microorganism [73].

Rotaviruses are the major causative agent of acute gastroenteritis in infants and children worldwide. However, to date, no specific antiviral drugs for the treatment of rotavirus infection have been developed. *L. plantarum* LRCC5310, more specifically the exopolysaccharides produced by these cells, were shown to have an antiviral impact against human rotavirus. The oral administration of exopolysaccharides for 2 d before and 5 d after mouse infection with the murine rotavirus epidemic diarrhoea of infant mice strain led to a decrease in the duration of diarrhea and viral shedding and prevented the destruction of enteric epithelium integrity in the infected mice. The authors demonstrated that the exopolysaccharides extracted from *L. plantarum* LRCC5310 can be utilized for the control of rotavirus infection [74].

In another study, a significant increment in the viabilities of macrophages were reported in the presence of *L. rhamnosus* before and after herpes simplex virus type 1 (HSV-1) infection when compared with *E. coli* as a non-probiotic bacterium. Results indicated that *L. rhamnosus* enhanced macrophage viability for HSV-1 elimination and activation against HSV-1 more effectively when compared with non-probiotic *E. coli* [75].

Conclusions

Probiotics are non-pathogenic microorganisms that are useful for human health. In the past, probiotics from various sources have shown tremendous applications as antimycobacterial, anticancer, and antiviral agents. Probiotics are known to exhibit anti-mycobacterial activities by inhibiting the synthesis of cell wall, reducing the constituents of proton motive force, and targeting ATP-dependent protease of the bacterium. Probiotics are considered potential anticancer agents due to their ability to produce metabolites that regulates apoptosis and confer protection against carcinogens. On the other hand, the antiviral activities of probiotics are limited to certain viruses, but it targets viral proteins to

inhibit the multiplication of virus. However, more research activities are required to understand the pivotal role of probiotics as therapeutics in the future.

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