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REVIEW ARTICLE

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Overview of Anticancer activity of Lactic Acid Bacteria

Desalegn Amenu Delesa

Jimma University, College of Natural Science, Biology Department, Jimma, Ethiopia, P.O.Box. 378

ABSTRACT

Cancer vestiges one of the leading causes of deaths worldwide despite its advances treatment and detection and the conventional chemotherapeutic agents used for the treatment of cancer have non-specific toxicity toward normal body cells that cause various side effects. In addition, cancer cells are known to develop chemotherapy resistance in due course of treatment, so, it's difficult and not easy to treat cancer using normal antiviral drugs. Thus, the demand for novel anti-cancer agents is increasing important to develop novel biological control approach. Some research reports have shown the therapeutic potential of LAB against various types of cancer cell lines. This makes them promising candidates for further investigation and clinical treatments. While a myriad of healthful effects have been attributed to lactic acid bacteria (LAB), perhaps the most controversial remains that of anticancer activity. The precise mechanisms by which LAB may inhibit any cancer are currently unknown. However, such mechanisms might include: alteration of the metabolic activities of intestinal microflora; alteration of physico-chemical conditions in the colon and gut; binding and degrading potential carcinogens; quantitative and/or qualitative alterations in the intestinal microflora incriminated in producing putative carcinogen(s) and promoters; production of antitumourigenic or antimutagenic compounds; enhancing the host's immune response; and effects on physiology of the host. In this review article, we present the overview of anticancer activity of the lactic acid bacteria.

Keywords: Metabolic Activities, Intestinal Microflora and Physico-chemical Conditions.

INTRODUCTION

Cancer is one non-communicable diseases and it's the major causes of morbidity and mortality throughout the world (Ferlay et al., 2013). Cancer cells are altered self-cells which have escaped normal growth regulating mechanisms. But due to environmentally induced or inherited genetic mutations, cells stop responding to normal growth control mechanisms and give rise to clones of cells that expand to considerable size, producing tumor or neoplasm (Hanahan and Weinberg, 2011).Some research reports indicated that species of LAB isolated from different sources possess certain anticancer activity and property (Kim et al., 2011). LAB have antitumor properties that inactivate or inhibit carcinogenic compounds in the gastrointestinal tract, stimulate the immune response, and reduce the enzymatic activity of β-glucuronidase, azoreductase, and nitroreductase, which are known to convert precarcinogens into carcinogens (Vamanu et al., 2006). Likewise, LAB have been shown to increase colonic NADPH-cytochromeP-450 reductase activity (Pool-Zobel et al., 1996) and glutathione S-transferase levels (Challa et al., 1997). Additionally, they have been shown to reduce hepaticuridine diphosphoglucuronyl transferase activity, which is involved in the metabolism of carcinogens in rats (Abdelaliet al., 1995).In addition to the anticancer properties of LAB discussed above, recent findings showed that LAB also exerts antiproliferation activities of colon cancer cells through synergistic actions between adherences to cancer cells and SCFA bio production (Azcárate- et al. 2011).

To prevent cancer cells, several mechanisms have been suggested,such as elevation of the hosts immune response, binding and degradation of potential carcinogens, qualitative alterations in the intestinal microflora that produce putative carcinogens and promoters (e.g., bile–acid degrading bacteria), production of antitumorigenic orantimutagenic compounds in the colon, and alteration of the metabolic activities of intestinal microflora (Hirayama and Rafter, 2000; Kim et al., 2008).The strategies available for the treatment of cancer are chemotherapy, surgery and radiation out of which chemotherapy is the main choice of treatment. But most of the time , chemotherapeutic drugs which target actively dividing cells are often associated with drug-induced damage to healthy cells and tissues, as they do not specifically target the cancer cells. Secondly, cancer cells frequently become resistant to chemotherapy due to various factors such as increased expression of drug detoxifying enzymes and drug transporters, and due to increased ability to repair DNA defects in cellular machinery that mediate apoptosis (Raguz and Yagüe, 2008).Therefore, there is an urgent need for cancer cell-specific targeted therapies that can alone treat cancer or can be used as adjuvants to lower the therapeutic doses of conventional anticancer drugs. With the growing popularity of peptide therapeutics, the scientific community has started exploring bacteriocins as novel therapeutic agents against cancer. The effects of bacteriocins on mammalian cells have been reviewed earlier (Cornut et al., 2008). In this review, latest studies on the anticancer properties of LAB have been summarized against cancer cells as compared to normal cells.

Anticancer properties of LAB

Recently, certain LAB have been reported to possess certain anticancer properties. Most studies, however, have focused on the effects of lactobacilli with regard to the reduction of cancer cell viability or tumour size (Kim et al., 2002 and Lee et al., 2004). Affording to research finding of (Salminen et al., 1993), oral administration of *Lactobacillus rhamnosus* was shown to lower the faecal concentration of β -glucuronidase in humans implying a decrease in the conversion of procarcinogens to cancinogens. Chiu *et al*., (2010) described bacterial soluble factors secreted by *Lactobacillus casei* and *L. rhamnosus* induced apoptosis

of human monocytic leukemia-cell line. Studies on antimutagenic activity of milk fermented with mixed-cultures of various lactic acid bacteria and yeast, showed that the fermented milks produced with mixed cultures of lactic acid bacteria had a wider range of activity against mutagens than those produced with a single strain of lactic acid bacteria (Tamai; et al., 1995). Similar results were found by Nandhini and Palaniswamy, 2013 in which anticancer activity of goat milk hydrolysate fermented by *Lactobacillus plantarum* and *Lactobacillus paracasei* was studied. Choi *et al* 2006, have evaluated the inhibitory effects of Lactobacillus (*L. acidophilus* 606 and *L. casei* ATCC 393, *L. rhamnosus* GG and *L. brevis* ATCC 8287) on various human cancer cell lines. The anticancer activities of the peptidoglycans or membrane components of the cell walls of various LAB strains, including Lactobacillus, have also been assessed (Kim et al., 2002). In the study carried out by Choi *et al*., 2006, the soluble polysaccharide fraction of the HK cells of *L. acidophilus* was found to inhibit cancer cell proliferation. Moreover, these polysaccharides proved to be much less cytotoxic to normal cells than the whole HK cells of the same strain. Wang *et al*., 2014, evaluated *in vitro* antitumor activity of c-EPS produced by *L. plantarum* and result demonstrated that c-EPS significantly inhibited the proliferation of HepG-2, BGC-823, especially HT-29 tumor cells. The results suggested that the c-EPS produced by *L. plantarum* 70810 might be suitable for use as functional foods and natural antitumor drugs.

In a mouse model, De LeBlanc *et al.2005,* demonstrated that 7 days of cyclical feeding with milk fermented with *Lb. helveticus* R389 resulted in a delay of tumor development, which was related principally to a decrease in the cytokine IL-6, normally implicated in the synthesis of estrogen in both normal and tumor-invaded breasts in mice, and an increase in the cytokine IL-10. Hence, different isolates of LAB have a potential towards prevention and control of cancer cell and tumor cell proliferation as we observed from above discussion and reports. The potential role of LAB has been extensively reviewed elsewhere (LeBlanc et al., 2002) and their beneficial effects include reinforcement of the natural defense mechanisms and protection against gastrointestinal disorders. Several publications have indicated that LAB plays an important role in prevention of cancer cell proliferation and developments (LeBlanc et al., 2002). Although there is no general consensus on the role of LAB in anticancer treatment, it is generally agreed that specific LAB strains can beneficially activate anticancer mechanisms, thereby regulating the host's immune response (Korhonen 2006).

LAB in preventing colon cancer

As some scholars present that ,treatment and management of cancer is one of the hot issues throughout the word both in developing and developed country in these days (Ilayas and Qadir, 2010; Tabasum and Qadir, 2010; Bokhari *et al.,* 2012; Farooqi *et al.,* 2013; Saleem *et al.,* 2013). Some stains of LAB like *Lactobacillus delbrueckii subsp. Bulgaricus* have potential activity as anti-mutagenic effects because they have ability to bind with heterocyclic amines which are carcinogenic (Wollowski *et al.*, 2001). Animal studies proved beneficial effects of LAB against colon cancer of rodents. Some studies on Human trials also suggest that some types of LAB are anti-carcinogenic due to their ability to decrease the activity of enzyme called β glucuronidase (Brady *et al.*, 2000) (which can generate cancer producing substances in the digestive system).

Lactic acid bacteria are known to be beneficial not only balance of intestinal flora but also for their antimicrobial, antioxidant, anti-inflammatory and anticancer effect (Dethlefsen et al., 2008). A recent study found antiproliferative effects of the cell-free filtrate and the cell-free lyophilized filtrate of LAB (*Pediococcus pentosaceus, Lactobacillus plantarum,* and *Weissella confusa*) on human colorectal adenocarcinoma cell (Knecht et al., 2014).

Increasing evidence also suggested that LAB including L. *casei* (Bignardi, 1998), *L. rhamnosus* (Assallo et al., 2014), *L. acidophilus*, all have the abilities of inhibiting tumor growth in rodents. Kahouli et al reported that*L. fermentum* NCIMB5221 was potent in suppressing colon cancer cells and promoting normal epithelial coloncell growth by the production of short chain fatty acids(SCFAs). Thirabunyanon and Hongwittayakorn (2013), reported *Pediococcus pentosaceus* FP3, *L. salivarius* FP25, *L. salivarius* FP35, and *Enterococcus faecium* FP51 isolated from new born feces showed antiproliferation of colon cancer. Lee NKet al (2008) reported *Lactococcus lactis* KC24 isolated from kimchi have anticancer activities against gastric carcinoma (AGS), colon carcinoma (HT-29 and LoVo),breast carcinoma (MCF-7), and lung carcinoma(SK-MES-1) cells (>50% cytotoxicity). Sevda ER et al, reported the effect of cell-free filtrate and cell-free lyophilized filtrate of *Pediococcus pentosaceus*, *Lactobacillus plantarum* and *Weissella confusa* inhibit the growth of colon cancer cellin a dose-dependent manner, by using MTTassay and *L. plantarum* showed the strongest inhibitory effect. Similarly, Ewaschuk et al, reported that *L. acidophilus*, *L. bulgaricus*, *L. casei*, *L. plantarum*, *Bifidobacterium breve*, *B. newbornis*, *B. longum* and *Streptococcus thermophilus* reducedthe viability and induced apoptosis of human colon cancer, HT-29 and Caco-2 cells demonstrated by DNA ladder assay. From the above findings, it is possible to conclude that, strains of lactic acid bacteria exhibited anticancer activity and not toxic to normalcells; however, the further study on the mechanism ofaction and other properties of these strains are neededto be investigated.

Effects of lactic acid bacteria on colon cancer may vary from strain to strain. Some strains may be helpful in minimizing mutagenic threat and other may potentiate this abnormality. Hence it is obvious to conclude here that augmentation of this cancer may be dependent of strain type or colonization of certain type of bacteria (Herrea et al., 2009). H_2O_2 involved in the increased proliferation and spread of cancer in colon, if this H_2O_2 level is reduced by any mean, it is possible to control or minimize the progression and spread of cancer within the colon area. This H_2O_2 level can be reduced by anti-oxidant activity in the particular area which in turn can be increased by catalase activity of the bacteria. If catalase producing bacteria will colonize more and more in the colon area it will increase antioxidant activity which ultimately reduces the risk of colon cancer. Blanc et al. (2008), have been shown that, *Lactococuss lactis* is the strain with this novel activity hence it can be used as potential controlling agent of colon cancer. On other hands, activity of LAB to prevent colon cancer may be intervention in different type of activities in the colon area. This may result in significant alterations of the composition of the colonic bacterial ecosystem, which consequently change metabolic activity of this organ. Regarding to the evidence of LAB protection against adinocarcinoma of colon is strengthened by the findings of Burns and Rowland after their extensive study on LAB and adenocarcinoma cells. They reported that, *Streptococcus thermophilus* and *Lactobacillus plantarum* are strains which protect normal cellular DNA from damage. Other strains of LAB including, *Lactobacillus bulgaricus* and *Enterococcus faecium* also possess anticarcinogenic activity but reason is not clear (Burns & Rowland, 2004). Another study conducted by Tavan et al. suggested that anticarcinogenic effects of *Streptococcus thermophilus* were due to inhibition of major mutagenic molecule i.e. heterocyclic aromatic amines (Tavan et al., 2002). Orlando et al. (2009) have shown the anticancer effects of another lactic acid bacterium *Lactobacillus rhamnosus.* Kim et al. (2003) in their study described that *Lactococcus lactis* possesses anticolonic cancer activity because of its ability to increase the level of antiproliferative protein and decrease the effects of mutagenic protein more these organism can be given orally. Anotherstudy

confirmed the effectiveness of lactic acid bacteria in colon cancer (Purhit et al., 2009). From the argument up till now it is clear that LAB has a significant role in antiproliferation, metastasis, growth and development and spread of colon cancer. From these findings it has been concluded that LAB has a unique role in colon cancer. Various strains of LAB are effective orally or any other route of administration. They can be used live or attenuated. Immunization against colon cancer can be done with the help of LAB.

Immune responses induced by lactic acid bacteria

The immune system plays a critical role in control of infectious diseases and pathogens proliferation, especiallytumor promotion and progression (Uccello et al., 2012). he interaction of several elements of the immune system, such as antigen presentingcells (APCs), different subsets of T cells, Bcells, natural killer (NK) cells, and dendritic cells (DCs), isusually activated by damage, invasion or mutation (Jounai et al., 2012). Recent studies implicate LAB in immune responses criticalfor colorectal cancer prevention and therapeutics (Gabrilovich and Pisarev, 2003), especially the Lactobacillus species, can potentially play a significant role in the antiviral and antimicrobial activity as an important contributor to the host's immune system. L. plantarum strain YU, isolated from food products, showed high interleukin 12-inducingactivity in mouse peritoneal macrophages (Kawashima et al., 2012) and the strain enhanced natural killer cell activity in spleen cells and production of IgA from Peyer's patch cells. Furthermore, activation of Th1 immune responses and IgA production induced anti-influenza virus H1N1 activity (Kawashima et al., 2012).

Antioxidant Activity of LAB

LAB considered as a bio active safe microorganisms that normally transit the gastrointestinal tract and colonized intestinal microbial ecosystem promoting host health a (Chu-Chyn et al., 2009) and they are generally considered as SAFE. Although survival LAB is higher for intestinal strains, certain numbers of these bacteria are lysed and their intracellular extracts released into the gut (Isolauri et al., 2004). Therefore, it is of interest to compare their antioxidative ability of intact cells and both extra- and intracellular extracts of LAB strains. It suggests that the level of antioxidant factor in the intracellular extracts was greater than that released in the medium. Saide and Gilliland (2005) have been reported that intracellular extracts of lactobacilli possessed markedly increased antioxidative activity than intact cells.Since it has been indicated that *Lactococcus* expresses activity of antioxidative enzyme superoxide dismutase (SOD) (Sanders et al., 1995), it is possible that the significant increase in inhibitory activity of the intracellular extracts could be due to the greater accessibility of anti-oxidative enzymes to the oxidant substrates. According to Lin and Yen (1999), the intracellular extracts of lactic acid bacteria have metal ion chelating ability, reactive oxygen species scavenging ability and reduction activity. Although, conditions in the gastrointestinal tract are very complicated, the study of Kaizu et al. (1993) demon-strated that the intracellular extract is also antioxidative *in vivo*. In addition, Kaizu et al. (1993) have demonstrated that haemolysis of red blood cells was inhibited in rats which were administered with the intracellular extracts of *Lactobacillus* sp. The reports provided evidence that the intracellular extract is antioxidative and improved the α-tocopherol deficiency status. Therefore, as the above mentioned research reports indicate, LAB stains are promising sources of potential antioxidant and may be efficient as preventive agents in some diseases specially cancer and tumor cells.

Antiviral activity of LAB

Emerging resistance to antiviral agents is a growing public health concern worldwide as it was reported for respiratory, sexually transmitted and enteric viruses. Therefore, to

overcome and reduce this problems it needs a growing demand for new, unconventional antiviral agents which may serve as an alternative to the currently used drugs. Some literature shown us as advantages and potency of lactic acid bacteria (LAB) and their bacteriocins as antiviral agents.Health-promoting LAB probiotics may exert their antiviral activity by (1) direct probiotic–virus interaction; (2) production of antiviral inhibitory metabolites; and/or (3) via stimulation of the immune system (Lehtoranta et al., 2014). LAB with protective effects against viral respiratory infections in mice and humans have been reported (Guillemard et al.,2010 and Maeda et al., 2009) and It established that oral daily administration of L. plantarum L-137, a strain with proinflammatory activity, decreased influenza virus H1N1 titers in lungs of infected mice (Maeda et al., 2009). Similarly, Boge et al.,2009 and Olivares et al., 2007) in their studies showed that *L. fermentum CECT5716* and *L. casei DN114-001* enhanced the effects of vaccination against influenza virus and improved antibody responses to influenza virus vaccination in humans, respectively . On other hand, Boge et al. 2009, demonstrated that the daily consumption of a probiotic-fermented dairy drink improved antibody responses to influenza virus vaccination in the elderly in two randomized, controlled trials. These successful preclinical and clinical trials highlight the potential of LAB probiotics as preventive and therapeutic agents in RVI. Protective effect achieved by strain CRL1505 was related to its capacity to modulate respiratory antiviral immune response by secretion of IFN-c and IL (Salva et al., 2013). In direct line, Chiba et al. 2013, showed that oral administration of L. rhamnosus CRL1505 to of BALB/cmice permitted a protective effect by modulating pulmonary innate immune microenvironment. The use of LAB as antiviral agents is relevant for agriculture poultry industry and medical applications for treatment of various viral infections.

Cytotoxic effects of lactic acid bacteria

Some research reports revealed that selected species of LAB isolated from animals, plants and some fermented foods have shown cytotoxic effects on cancer cells and tumor cells. *Lactobacilli* and *Bifidobacteria* are the most prominent lactic acid bacteria, and have been accepted as the reason for the increasing research attention on the prevention of cancer (Wang et al., 2014). The different fractions of LAB, such as whole cells, heat-killed cells, the cell wall, peptidoglycan, and cytoplasmic fraction, all have preventive effects against human cancer cell lines (Kim et al., 2003). Furthermore, it has been reported that polysaccharide fractions originating from *Lactobacillus* cultures and glycoproteins found in the supernatants of *Lactobacillus* cultures have the same effect. Sevda et al (2015), evaluated the ant proliferative effects of the cell-free filtrate and the cell-free lyophilized filtrate of 3LAB (*P. pentosaceus*, *L. plantarum*, and *W. confusa*) on the human colorectal adenocarcinoma cell line. Paolillo *et al.* (2009) studied the cytotoxic effect oflive cells of *L. plantarum* on Caco-cells. A dose-dependent response has been reported for the anticarcinogenic and/or antimutagenic abilities of some LAB strains (Salminen et al., 1998). Generally, P*. pentosaceus*, *L. plantarum*, and *W. confusa* have the potential to inhibitthe proliferation of Cancer cells. *L. plantarum* showed the strongest inhibitory effect. Although there are anticancer studies with *L. plantarum* (Kim et al., 2002; Paolillo et al., 2009), there are not adequate data regarding the anticancer effects of *P. pentosaceus* and *W. confusa*. Patel et al. (2010) reported that dextran isolated from *P. pentosaceus* possesses potential as a gelling agent in food formulations and as a drug delivery carrier, tissue engineering scaffold, and as a biomaterial for various other biomedical applications (Patel et al., 2010). Additionally, Villarante et al. (2011) revealed that bacteriocin isolated from *Pediococcus acidilactici* has a cytotoxic affect onHT29 (human colon adeno carcinoma) and HeLa cellsas

detected by MTT assay. In the modern era, there is a demand for such foodsas functional foods, pharma foods, and nutraceuticals for preventing diseases (Khan, 2014). Increasing interest has stimulated innovation and new product development inthe food industry around the world (Vinderola, 2008). More work is needed in order to revealthe causative underlying characteristics responsible for specific antitumor effects.

LAB in Inhibition of tumor cell proliferation.

LAB have different medical application in prevention and control of cancer such as colon cancer, and they have ability to inhibit disease via modulation of the mucosal andsystemic immune response and by reduction of the inflammatory response to host microbiota (Loredana et al., 2012). Not only can this but also, hey prevent tumor cell via the activation of immunity by immune cells to fight with the tumor cells, delay the onset of tumor or increase the survival rate. Galdeano et al. (2007), analyzed the profile of cytokines induced by someLAB strains and observed that the most remarkable effectfor all the LAB strains tested is the increase inTNF-α, interferon-γ (IFN-γ) and the regulatory cytokineIL-10. As Lee et al 2004, LAB such as L. acidophilus, Lactobacillus casei (L.casei) and B. longum have been shown to possess immunomodulatory and antitumor effects by suppressing theproliferation of tumor cells and prolonging survival. The increase in survival was correlated with an increase incellular immunity as reflected by the enhancement in thetotal numbers of T cells, NK cells and MHC class Ⅱ cells, and CD4-CD8+ T cells in flow cytometry analysis. Similarly, several strains of LAB have been shown to exert powerful anti-tumor effects, especially L. casei Shirota has been shown to exert strong anti-metastatic effects ontransplantable tumor cells and to suppress chemically induced carcinogenesis (Takagi et al., 2001). Taken together, these review provide convincing evidence demonstrating the important role ofLAB and their byproducts in the protection against carcinogenesis processes. Long-term controlled studies are required, however, to ascertain the benefits of dietary lactobacilli in preventing or alleviating cancer in human subjects.

LAB Induction Apoptosis

Apoptosis is a form of genetically programmed cell death, playing a key role in the regulation of cell numbers. An important pathogenetic event in many types of cancers is the reduced ability to triggerapoptosis associated with alteration of control processes of cell proliferation (Elmore, 2007). The regulation of cell survival and death at molecular level on the apoptotic process can have a huge chemopreventive and therapeutic potential (Fesik, 2005). Several studies showed that LAB can play a role in the regulation of cell apoptosis *via* intrinsic and extrinsic pathways which are potentially critical mechanisms in the prevention of cancer cell. Chen *et al. (*2013) analyzed the effect oforal administration of *Lactobacillus acidophilus* (*L. acidophilus*) on colorectal cancer in mice. Their results indicated that *L. acidophilus* reduced the severity of colorectal car cytogenesis and enhanced apoptosis in treated mice. Ithas been shown that *Lactobacillus reuteri* (*L. reuteri*) may prevent colorectal cancer *via* down regulating nuclearfactor-kappaB (NF-κB)-dependent gene products which regulate cell proliferation (Cox-2, cyclin D1) and survival (Bcl-2, Bcl-xL) (Iyer et al., 20 08). Furthermore, *L. reuteri* suppressed tumornecrosis factors (TNF)-induced NF-κB activation including NF-κB-dependent reporter gene expression in a dose- and time-dependent manner to slow down cancer cell growth. Therefore, an improved understanding of probiotics-mediated effects on apoptosis signaling pathways is critical for development of future LAB-based CRC treatments.

LAB in Diseases Management

As the most common types of microbes used as probiotics, LAB are comprised of an ecologically diverse group of microorganisms united by formation of lactic acid asthe primary metabolite of sugar metabolism, including *Lacto bacillus*, *Streptococcus*, *Enterococcus*, *Lactococcus*, *Bifidobacterium* and *Leuconostoc* (Masood et al,2013). Their beneficial effects were initially revealed by E. Metchnikoff (1845-1919), a Russian scientist who proposed that extended longevity ofthe people of Balkan could be attributed to their practice of ingesting fermented milk products. Recent studies showed that LAB could be successfully used to manage diarrhea [Chouraqui et al 2004, Gaón et al., 2003], food allergies (Pohjavuori et al.,2004) and inflammatory boweldisease (IBD) (Bourlioux et al., 2011; Azcárate et al.,2011 and del Carmen et al .,2011).Lactobacillus GG strain has been to be very effective against viral and idiopathic diarrhea as identified by Harish andVargese in their studies (Harish and Vargese, 2006).Canani et al. (2007) investigated the effects of lactic acid bacteria (*Lactobacillus rhamnosus*, *Lactobacillus plantrum, Bifidobacterium,* and *Enterococcus faecium*SF68) on children of 6 to 36 months of age with diarrheal complication and found that these were effective in preventing diarrheal complications. *Bactobacillus G G* was found to be more effective anti diarrheal agent Streptococcus faecium strain SF68 was effective against diarrhea associated with respiratory tract infection. Due to these beneficial effects of lactic acid bacteria in Diarrheal disease especially in children, use of LAB containing food such as yogurt and fermented milk should be promoted in children.

According to Myllyluoma et al. (2007), in their study reported the beneficial effects of Lactic acid bacteria in gastric ulcer and this is due to the destructive actions of lactic acid bacteria on *H. pylori*. If LAB are used in combination of antiulcerative therapy then results are astonishingly fast recovery and improved efficacy of therapy. Again Myllyluoma et al., (2007) revealed that, Lactococcus *rhamnosus* not only is used as adjunct in anti-ulcerative therapy but also reduced ethanol-induced mucosal lesion. Pre-treatment with *Lactococcus rhamnosus* also significantly increases the basal mucosal prostaglandin E2 (PGE2) level, also attenuates the suppressive actions of ethanol on mucus secreting layer and transmucosal resistance and reduces cellular apoptosis in the gastric mucosa. Hence we can say *Lactococcus rhamnosus* is an antiulcerative in many ways as reported by researchers (Lam et al., 2007).

LAB also play a vital role in minimizing allergic responses this due to its situations potentiation of its responses (Azizpour et al., 2009). It has been found that *Lacticbacillus citreum* regulates serum IgE generation controls over-all antibody production. *Lactobacillus citreum* can be useful in preventing the development and progression of IgE production. Hence it is possible to prevent hypersensitivity reactions by the use of this microbe (Kang et al., 2009). Anti-allergy immuno-regulation by LABhas been developed in recent years. There are evidences that suggest that *Enterococcus faecalis* could relieve theclinical symptoms of Japanese cedar pollinosis. Shimada et al. (2004) has demonstrated an improved clinical symptomsin allergic rhinitis. Enterococcus role was investigated in eospinophil aggregation. It can be concluded here that Enterococcus may play a role in alleviation ofallergic reactions (Shimada et al., 2003).

LAB Antiviral Agents and its mechanism of action

Hydrogen peroxide (H_2O_2) produced by Lactobacillus sp. plays an important role as a natural microbicide within the vaginal ecosystem and is toxic to a number of organisms, including human immunodeficiency virus type 1 (HIV-1) and HSV-2 (Conti et al., 2009). Lactic acid, a final product of carbohydrate metabolism, is produced by all Lactobacillus species and is

responsible for the homeostasis of the vaginal pH (B4.5). Acidic pH inactivates HIV (Martin et al., 2010) and HSV-2 (Tuyama et al., 2010). Moreover, HSV-2 is irreversibly inactivated by concentrations of lactic acid at the pH value corresponding to that observed in the healthy human vagina (Conti et al., 2009).It is appearing that lactobacilli could produce compounds that could help the host cells to defy viral replication(Mastromarino et al., 2011). Related to this, a non-protein cell wall component extracted from a vaginal strain of L. brevis strongly reduced HSV-2 replication in cell culture (Mastromarino et al., 2011), whereas acid Lactobacillus metabolic products decreased activation of T lymphocytes, which may result in decrease in lymphocyte susceptibility to HIV-1 infection.

Bacteriocins are ribosomally synthesized small, mostly cationic, amphiphilic peptides, with antimicrobial properties directed against closely related bacterial species (Ennahar et al., 2000). It should be noted that antagonism against distant organisms was also reported, but very rarely. Originally, four classes of bacteriocins were proposed based on their biochemical and genetic characteristics, structures and mechanisms of action. Cotter et al. (2005), reclassified bacteriocins and suggested only two simplified groups i.e., Class I, lantibiotics and Class II, non-lantibiotics. Most bacteriocins actby forming pores in the membranes of target cells (Humaira et al., 2006), causing a decrease in the intracellular pH and inhibiting enzymatic processes. Class I bacteriocins (lantibiotics), such as nisin, have been shown to bind to lipid II, themain transporter of peptidoglycan subunits from the cytoplasm to the cell wall, and therefore prevent correct cell wall synthesis, leading to cell death (Cotter et al., 2005). Furthermore, they can use lipid II as a docking molecule to initiate a process of membrane insertion and pore formation that leads to rapid cell death (Cotter et al., 2005). Class II encompasses subclass IIa (pediocin-like bacteriocins), subclass IIb (two-peptidebacteriocins) and subclass IIc (circular bacteriocins).

Antiviral activity by enterocin CRL35 and ST4V has been observed against thymidine-kinase positive and deficient strains of HSV-1 and HSV-2 in Vero and BHK-21cells, affecting intracellular viral multiplication, and inhibiting late stages of replication (Todorov et al., 2005; Wachsman et al., 2003 and Emiliano et al.,2007). Remarkably, the amino-acid sequence of CRL35 is expected to play a role in anti-HSV-1 and anti-HSV-2 activities. Derivatives of CRL35 without at least two cysteine residues were assayed and shown to be devoid of antibacterial activity; and the authors hypothesized that these derivatives will bedevoid of antiherpes activity as well (Emilianoet al., 2007). Therefore, LAB have a potential ability to prevent and reduced tumor cells and they have high potential of antiviral activity, further more in order to investigate detail mechanism of LAB in preventing and control proliferation and development of tumor cell and colon cancer cells it needs more investigation.

CONCLUSION

The use and application of LAB and their constituents for antiviral agents is a promising path in search for novel unconventional treatments and prevention strategies to prevent cancer and tumor cells. This review paper highlighted the main mechanisms of virus inactivation by LAB towards prevention and controlling of tumor cell and virus proliferation and development. Further, combination of LAB and their products with traditional antiviral drugs may result in discovery of synergistically acting compositions and useful formulations for treatment of some viral infections. There are several possible mechanisms that may explain how LAB may protect against tumour and cancer cells development. It is possible that different strains of LAB target different mechanisms. More work needs to be done to

identify the specific strains and strain characteristics responsible for specific antitumour effects and the mechanisms by which these effects are mediated. In addition it needs more investigations are needed to understand the mechanisms of the inhibitory effects on cancer cells and other details for application use.

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Corresponding author: Desalegn Amenu Delesa (M.Sc.), Jimma University, College of Natural Science, Biology Department; Jimma; Ethiopia, P.O.Box.378
Email: wadadesalegn@gmail.com