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# Role of probiotics in the management of lung cancer and related diseases: An update

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ABSTRACT

Worldwide, lung cancer remains to be the most common cause of cancer-related deaths. A wealth of data has shown that probiotics play essential roles in different types of tumor prevention and treatment. However, data specifically linking probiotics with lung cancer is very limited. This review summarizes the utilization of probiotics directly for the treatment by mentioning *in vivo* and *in vitro* case studies, and also indirectly by discussing their impact on various causes responsible for lung cancer growth and thus playing important role in the prevention of cancer. The main findings of the review include that with probiotics treatment better survival rates with an augmented expression of tumor suppression genes were obtained. However, the expression of two oncogenes studied was found to be decreased, whereas increased cytotoxic effects were also observed in lung cancer cells. In addition, protective mechanism of probiotics was supposed to be linked with immunomodulation.

## 1. Introduction

Worldwide, Lung cancer is the most common cause of cancer deaths (1.8 million), estimated to be responsible for nearly one in five deaths (Chen, Zheng, Zeng, & Zhang, 2015). It has been found to be the leading cause of cancer death among males and the second leading cause of death in females globally (Torre et al., 2015), and is responsible for 19.4% of all cancer deaths (Chen et al., 2015). Based on their morphological features of cancer cells, there are two major types of lung cancer: small cell lung cancer (SCLC; 18%), which grows more quickly and shows metastasis (more likely to spread) to other organs of the body, and non-small cell lung cancer (NSCLC; 78%), which develops and spreads slowly, and is further classified into three types, namely squamous cell carcinoma (25%), adenocarcinoma (40%), and large cell lung cancer (10%). With regard to other histological types of lung cancer, the incidence of squamous cell carcinoma and small cell carcinoma has been decreasing, while that of adenocarcinoma has been increasing in both men and women (Toyoda, Nakayama, Ioka, & Tsukuma, 2008). According to many studies, genetic factors (Lu et al., 2013), smoking, pollution from transport (Vineis et al., 2006), toxic heavy metal consumption, exposure to radon gas (in mines or homes) (Zhang et al., 2012), respiratory diseases, alcohol intake (Druesne-Pecollo et al., 2014) and exposure to asbestos, silica dust, and several elements (Islami, Torre, & Jemal, 2015) are responsible for the incidence of lung cancer. However, smoking has been found to be the major cause and accounts for 80–90% of all lung cancer cases (Alberg, Brock, Ford, Samet, & Spivack, 2013; Kim, Lee, et al., 2014; Kim, Kim, et al., 2014).

Over the past few decades, patients with early-stage lung cancer have shown significant improvements in their health. However, in spite of many therapeutic advances, it has been reported that the overall 5-year survival rate is confined to 15% for men and 21% for women (American Cancer Society, 2017).

Therefore, innovative strategies are required to prevent and treat lung cancer (Viktorsson, Lewensohn, & Zhivotovsky, 2014). The American Institute for Cancer Research and the World Cancer Research Fund have assessed that the food, nutrition, physical activity, and body composition play a central part in the prevention of cancer (WCRF/AICR, 2007).

It has been found that the gastrointestinal tract is a habitat for trillions of microbes, which are essential for maintaining immune homeostasis in the gut microenvironment (Lee, Kim, Han, Eom, & Paik, 2014; Serban, 2014). According to the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), probiotics are defined as live microorganisms, which when administered in adequate amounts, confer a health benefit on the host

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(FAO/WHO, 2001; Fijan, 2014). However, huge variations have been recorded in the health benefits of different strains of probiotics. Gut microbiota provides potential nutritional and health benefits, such as nutrient utilization, resistance against infections, manipulation of intestinal microbial communities, maturation of the immune system, and regulation of host metabolism (Brestoff & Artis, 2013; Hooper, Littman, & Macpherson, 2012). The composition of microorganisms present in the gut is highly variable to external influences such as age, diet, stress, illness, medications, and lifestyle (Sommer & Bäckhed, 2013). Moreover, it has been reported that changes in the gut microbiota may lead to many disorders, including obesity, asthma, inflammatory bowel disease, psychiatric problems, and cancers also (Yu & Li, 2016).

Worldwide, cancer incidence and mortality rates have increased over the past decade; therefore, the protective role of probiotics against various cancers has fascinated the scientific community. Several epidemiological pieces of evidence have been reported about the use of probiotics in the prevention and treatment of different types of cancer (Kumar et al., 2010). The possible pleiotropic health effects of probiotics in eliciting anti-microbial and anti-tumor effects (Kumar et al., 2010) include delaying tumor growth, improving host immunity (innate and adaptive), getting free of various mutagens by competitive binding and degradation, decreasing the side effects of chemotherapy by metabolic activity improvement, direct inhibition of foodborne pathogens by competition, and also help in the reduction of post-operative complications (Liu et al., 2017; Patel & Denning, 2013; Raman et al., 2013) and heavy metal sequestration. Nevertheless, many other useful modes of action of probiotics are still unknown. In a previous review, the possible strategies of probiotics for the prevention or treatment of various cancer cell types, i.e., colon & rectum, breast, blood, cervical, prostate & bladder, skin & esophagus, liver & gall bladder, and head & neck have been described (Dasari, Kathera, Janardhan, Kumar, & Viswanath, 2016). Nowadays, much attention is given to the use of probiotics in the treatment of lung cancer. However, very little literature is available about the link between probiotics and lung cancer. Considering the importance of probiotics, this review discusses our current understanding of (1) the direct effects of probiotics in lung cancer treatment, (2) the indirect possible roles of the impact of probiotics on respiratory diseases and their possible mechanisms of action in the lung cancerous cells (Fig. 1).

## 2. Direct impact of probiotics in treatment of lung cancer

It is essential to understand the composition of lung microbiota in both states of health and disease. For the accurate diagnosis and treatment of lung cancer, identification of novel therapeutic targets in the lung microbiome is crucial (Hooper et al., 2012). It is important to realize whether the microbe is directly involved in pathogenesis, or after disease occurrence, there is a reduction in the healthy microbial pool of the person. Though the evidences suggesting the role of probiotics in the prevention of lung cancer are still limited, still, some studies are showing the promising role of probiotics. A study has suggested that the well-balanced intestinal microflora play protective role in the treatment of cancer (Iida et al., 2013). In a recently reviewed literature, it has been proposed that with the help of metagenomics, metatranscriptomics and culturomics platforms, comparison of microbial composition in cancer patients and healthy volunteers is becoming practical. The data generated together can indicate which bacterial genera or species could be beneficial to patients (Zitvogel, Daillère, Roberti, Routy, & Kroemer, 2017). Therefore, cancer treatment with microbiome or their products has the potential to treat tumours. However, it has also been stated that the microbial agents could also negatively affect cancer prognosis through the production of potentially oncogenic toxins and metabolites by bacteria. Thus, future treatments would rely on the use of combination of microbiome and its products with immunotherapeutics and more conventional approaches to target directly the malignant cells (Zitvogel et al., 2017).

The coming section was describing the role of probiotics in treatment of patients with lung cancer, lung cancer-bearing mouse and few *in vitro* studies of lung cancer cell lines with other cancerous cells. Following this, a couple of studies describing the effect of probiotics on the lung metastasis, check point inhibitors, homeostasis, and elevated efficacy of anti-tumor drugs has been described. Finally, the approach of recombinant probiotic bacteria, i.e., *Bifidobacterium infantis* as a possible therapeutic agent against lung cancer has been described (Table 1).

Although there are not articles that showed the direct effect of probiotics against lung cancer in humans, one research described previously has used 30 lung cancer patients to check the possibilities of improvement in the gut bacteria of the patients receiving chemotherapy by using probiotic bacterial strains. One group (n = 21) which was given combined treatment of probiotic strain based on *Bacillus subtilis* together with chemotherapy course resulted in improvement in the intestinal microflora and decreased rate of intestinal dyspepsia was observed. Patients of the control group (n = 9) have only received chemotherapy, showed constipation and decrease quantity of *Lactobacillus*, *Bifidobacterium* and *Bacteroides* and an increase was observed in different pathogenic bacterial strains (Mlu et al., 2013). Using this (probiotic medicines + chemotherapy) in lung cancer patients is encouraging to decrease the frequency of gastrointestinal complaints and prevent deterioration of the gut microflora.

Lewis lung cancer (LLC)-bearing mice (C57BL/6J) were used as tumor models in one *in vivo* study depicting the use of probiotics. The lung cancer cells were subjected to three different treatments (Table 1) and divided into the following groups: cisplatin group, cisplatin/ABX (an antibiotic cocktail of vancomycin, ampicillin, and neomycin, which disturbs intestinal microflora homeostasis) group, and cisplatin/*Lactobacillus acidophilus* (probiotics) group. Results showed positive effects with decreased tumor size and better survival rates. In cisplatin and cisplatin/ABX groups, shorter survival rates were observed, as compared to cisplatin/*L. acidophilus* group, which showed longer survival rates in mice. In addition, the effect of the probiotic strain on two oncogenes (*Vegfa* and *Ras*) and two tumor suppressor genes (*Cdkn1b* and *Bax)* was also evaluated using western blotting. Decreased expression levels of *Vegfa* and *Ras*, and increased expression levels of *Cdkn1b* and *Bax* genes were observed. Additionally, this study showed an increased anti-tumor response in *Lactobacillus*-co-treated mice with upregulated interferon (IFN)-γ, Gzmb, and Prf1 mRNA expression (Gui, Lu, Zhang, Xu, & Yang, 2015). IFN-λ plays an important protective role against cancers, mediated by probiotics. As far as we know, this was the sole study reported for individual lung cancer tumor model and use of probiotic bacterial strain.

The other two studies included in this were performed *in vitro* on various cancerous cell lines including the lung cancer, and the direct effects of various probiotic strains were analyzed for various clinical studies (Table 1). A probiotic strain, *Lactococcus lactis* KC24 was used, and its anti-cancer effect on various cancer cell lines, including lung carcinoma (SK-MES-1), breast carcinoma (AGS and MCF-7), and colon carcinoma (HT-29 and LoVo) was determined. Results showed that all the cancer cells with $10^6$ CFU/well of *L. lactis* KC24 resulted in strong inhibition of proliferation using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Proliferation of SK-MES-1, AGS, MCF-7, HT-29, LoVo, and cells was inhibited by 86.53%, 90.12%, 91.89%, 68.30%, and 67.27% respectively (Lee et al., 2015).

In the same year, another study demonstrated that the probiotic strain, *L. lactis* NK34, exhibits anti-cancer and anti-inflammatory activity against various cancer cell lines, like SK-MES-1 (human lung carcinoma cell line; KCLB 30058), DLD-1 (human colon adenocarcinoma cell line; KCLB 30058), HT-29 (human colon adenocarcinoma cell line; KCLB 30038), LoVo (human colon adenocarcinoma cell line; KCLB 10229), AGS (human stomach adenocarcinoma cell line; KCLB 21739), and MCF-7 (human breast adenocarcinoma cell line; KCLB 30022). Cytotoxicity of the NK34 strain was observed in normal as well cancer

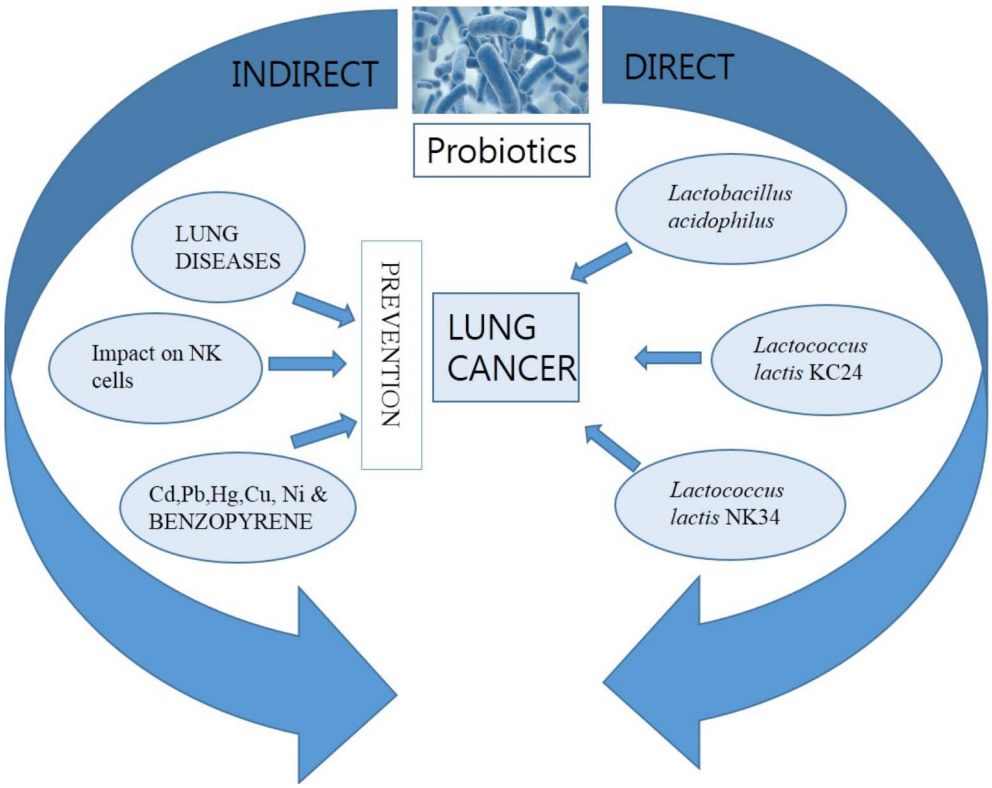


**Fig. 1.** Depiction of the direct and indirect effects of probiotics on lung cancer. Right section of the figure is representing the direct effect of probiotic bacterial strains, i.e., *Lactobacillus acidophilus*, *Lactococcus lactis* KC24 and *L. lactis* NK34 during an *in vivo* and *in vitro* studies. Left section of the figure representing the indirect beneficial effects of the use of probiotics for the prevention of lung cancers by treating lung and respiratory diseases and also clearing heavy metals and harmful chemicals from the body.

using MTT assay and morphology observation. Treatment of cancer cells with $10^6$ CFU/well of *L. lactis* NK34 resulted in strong inhibition of proliferation, i.e., SK-MES-1 (96.71%), DLD-1(77.23%), HT-29 (97.05%), LoVo (97.64%), AGS (82.07%), and MCF-7 (97.99%). In addition, the anti-inflammatory effect of *L. lactis* NK34 revealed a decrease in NO production and pro-inflammatory cytokines (Han, Lee, Park, & Paik, 2015). It can be observed that two strains of *Lactococcus lactis* namely KC24 and NK34 resulted in strong cytotoxic effect on lung carcinoma cell line (SK-MES-1), these encouraging results represented the potential use of probiotic as microbial therapy for the treatment of lung cancer.

Though this review is representing the recent literature about the use of probiotics in the treatment of lung cancer, it was worth mentioning that such type of experiments was started decades also. Before, the anti-tumor activity of *Lactobacillus casei* YIT 9018 (LC 9018) on Lewis lung carcinoma (3LL) in C57BL/6 mice and line-10 hepatoma in strain-2 guinea pigs was examined. *L. casei* YIT9018 has been shown to suppress pulmonary and regional lymph node metastases in mice and guinea pigs (Matsuzaki, Yokokura, & Azuma, 1985).

The augmented efficacy of anti-tumor vaccine (with probiotics or its products) was evaluated for solid sarcoma 37 (S37) and metastatic Lewis lung carcinoma (3LL). They have used probiotic mixture of *Enterococcus faecium* K-50 and *Saccharomyces cerevisiae* 14 K or their metabolic products. The results revealed that the combined application of antitumor vaccine with pro-and/or prebiotic resulted in synergistic effect in the therapy for S37-bearing mice and in 3LL-bearing animals combined application inhibited metastasis by 2 to 2.5-fold compared to animals treated by vaccine only (Tanasienko et al., 2005).

Another research demonstrated that the administration of fermented milk by *L. casei* CRL 431 to cancer BALB/c mice resulted in the reduction or inhibition of tumor growth with less tumor vascularity, extravasation of tumor cells, and lung metastasis. It was due to the immune response such as decreasing the infiltration of macrophages in both the tumor and the lungs and an increased $CD4^+$ lymphocytes and antitumor response associated to $CD8^+$ immune cells (Aragon, Carino, Perdigon, & de Moreno de LeBlanc, 2015).

One more study related to lung metastasis established that use of Kefir (a probiotic-containing fermented milk product) has been shown to exert cytotoxic effects on 4T1 breast tumor cells. Results exhibited that in a BALB/c mice treated with kefir water after 4T1 cancer cells transplantation, a significant improvement was observed in helper T cells and cytotoxic T cells as well as a reduction in metastasis to lung and bone marrow were detected (Zamberi et al., 2016).

Furthermore, another research described that the commensal bacteria are crucial in maintaining immune homeostasis by shaping the efficiency of immune surveillance in mucosal tissues. Authors reported that antibiotic-treated (Abt) mice were more susceptible to development of engrafted B16/F10 melanoma and Lewis lung carcinoma. The mice presented a shortened mean survival time with more numerous and larger tumor foci in the lungs. The investigation revealed that it was due to defective induction of the γδT17 cell response in the lungs of Abt mice. The γδT cells play important roles in the establishment of the tumor microenvironment and the development of tumor immunity. Addition of normal γδT cells or supplementing IL17 restored the impaired immune surveillance phenotype in Abt mice. Overall, the importance of commensal bacteria in supporting the host immune response against cancer was demonstrated (Cheng et al., 2014).

Sivan, Corrales, and Hubert (2015) have evaluated the role of gut microbiota in lung cancer therapy using immune checkpoint inhibitors. They have reported that the oral administration of a *Bifidobacterium* cocktail (*B. bifidum*, *B. longum*, *B. lactis*, and *B. breve*) on its own improved tumor control to the same degree as programmed cell death protein 1 ligand 1 (PD-L1)-specific antibody therapy (check point blockade) and together these two treatments nearly abolished tumor outgrowth. With *Bifidobacterium* treatment, improvement was seen in immune responses including CD8+ T cell activation and co stimulation, cytokine-cytokine receptor interaction, augmented dendritic cell (DC) function and the chemokine-mediated recruitment of immune cells to the tumor microenvironment.

Another research reported that the efficacy of CTLA-4 blockade depends on distinct *Bacteroides* (*B. thetaiotaomicron* or *B. fragilis*) species. Tumours in germ free mice did not react to CTLA-4 blockade.

**Table 1**
*In vivo* and *in vitro* effects of probiotics on lung cancer cells and lung metastasis.

| Cells/disease | Type of work | Probiotic strain/animal model | Results | References |
|---|---|---|---|---|
| Lewis lung carcinoma (3LL) and line-10 hepatoma | *In vivo* | *Lactobacillus casei* YIT 9018 (LC 9018) C57BL/6 mice and strain-2 guinea pigs | Prolonged survival period and inhibition of pulmonary metastases | Matsuzaki et al. (1985) |
| Solid sarcoma 37 and metastatic Lewis lung carcinoma (3LL) | *In vivo* | *Enterococcus faecium* K-50 and *Saccharomyces cerevisiae* 14K (Balb/c and C57B16 mice) | Prebiotic inhibited metastasis by 2 to 2.5-fold compared to animals treated by vaccine only | Tanasienko et al. (2005) |
| Lung cancer | *In vivo* | *Bifidobacterium infantis*-mediated sFlt-1 gene transferring system (recombinant) LLC C57BL/6 mice | Inhibition of the tumor growth and prolonged survival time of LLC C57BL/6 mice | Zhu et al. (2011) |
| Lung cancer | *In vivo* | *Bifidobacterium infantis*-mediated soluble kinase insert domain receptor (sKDR) (recombinant) LLC C57BL/6 mice | Tumor growth suppression by increasing the necrosis rate of the tumor, and prolonged survival time of the mice | Li et al. (2012) |
| LLC (Lewis lung carcinoma) and B16F10 lung metastases | *In vivo* | Commensal microbiota (C57BL/6 mice | Microbiota modifications following antibiotic treatment induced the loss of γδT cells producing IL-17A | Cheng et al. (2014) |
| Lung cancer | *In vivo* | *Lactobacillus acidophilus* (C57BL/6J mice) | Anti-tumor effect of cisplatin increased in combination with *L. acidophilus* and decreased in combination with ABX. Combined treatment of probiotics and cisplatin increased survival rates | Gui et al. (2015) |
| Lung cancer cells and breast cancer | *In vitro* | *Lactococcus lactis* NK34 | > 77% of cytotoxic activity | Han et al. (2015) |
| Lung, breast, and cervical cancer | *In vitro* | *Lactococcus lactis* KC24 | Strong cytotoxic effect, except in cervical cancer cells | Lee et al. (2015) |
| Melanoma | *In vivo* | Bifidobacterium cocktail (*B. bifidum*, *B. longum*, *B. lactis*, and *B. breve*) C57BL/6 mice | Tumour controlled to the same degree as PD-L1-specific antibody therapy (checkpoint blockade) | Sivan et al. (2015) |
| Metastatic melanoma (MM) or non–small cell lung carcinoma (NSCLC) | *In vivo* | *Bacteroides fragilis and* Germ Free (GF́) mice | Immunostimulatory effects of CTLA-4 blockade | Vétizou et al. (2015) |
| Breast cancer and lung metastasis | *In vivo* | *L. casei* CRL 431 BALB/c mice | Decreased tumor growth, with less tumor vascularity, extravasation of tumor cells, and lung metastasis | Aragon et al. (2015) |
| Breast cancer and lung metastasis | *In vivo* | Kefir as a probiotic-containing fermented milk BALB/c mice | Enhancement in helper T cells and cytotoxic T cells and significant decrease in metastasis to lung and bone marrow | Zamberi et al. (2016) |
| Advanced lung and ovarian cancer patients | *In vivo* | *Enterococcus hirae* and *Barnesiella intestinihominis* C57BL/6J mice | Increased cyclophosphamide-anticancer effects | Daillere et al. (2016) |
| Lung cancer and other types of cancers | Survey | Mixed probiotics | Out of 25, 60% patients were found negative and 40% were found positive for probiotics use | Ciernikova et al. (2017) |

When germ Free (GF) (antibiotic treated) mice was orally administered with *Bacteroides fragilis*, an augmented immune response was observed. This was due to the cross-reactivity of the bacterial and tumor epitopes, which directed restoration of the therapeutic response of GF tumor mice to CTLA-4 antibody treatment. This study described the key role of *Bacteroides* in the immunostimulatory effects of CTLA-4 blockade (Vétizou et al., 2015).

Daillere et al. (2016) reported the role of two bacterial species, *Enterococcus hirae* and *Barnesiella intestinihominis* in improving the efficacy of the most common alkylating immunomodulatory compound cyclophosphamide (CTX). It was observed that the specific- memory Th1 cell immune responses selectively predicted longer progression-free survival in advanced lung and ovarian cancer patients treated with chemo-immunotherapy. The two strains were represented as valuable "oncomicrobiotics".

Li et al. (2012) have demonstrated the use of recombinant *Bifidobacterium infantis*. For this research, *Bifidobacterium infantis*-mediated soluble kinase insert domain receptor (sKDR) prokaryotic expression system was constructed and 3 LLC mice models groups were used. Group a treated with saline, group b treated with recombinant *Bifidobacterium infantis* containing pTRKH2-PsT plasmid; and group c with recombinant *Bifidobacterium infantis* containing pTRKH2-PsT/sKDR plasmid. The quality of life and survival of mice were recorded. The better quality of life was recorded for mice in group c than in other two groups. The recombinant *Bifidobacterium infantis* containing pTRKH2-PsT/sKDR plasmid improved the efficacy of tumor growth suppression by increasing the necrosis rate of the tumor, and prolongation of survival time of the LLC C57BL/6 mice. The anti-angiogenesis effect was also evaluated by MTT assay *in vitro*. In another study, *Bifidobacterium infantis*-mediated sFlt-1 gene transferring system was constructed using electroporation and antitumor effect was investigated on Lewis lung cancer (LLC) in mice (Zhu et al., 2011). Soluble fms-like tyrosine kinase receptor (sFlt-1) is a soluble form of extra membrane part of vascular endothelial growth factor receptor-1 (VEGFR-1) that has antitumor effects. The gene transferring system successfully expressed sFlt-1 at the levels of gene and protein. This system significantly inhibited the growth of human umbilical vein endothelial cells induced by VEGF *in vitro*. In addition, tumor growth was inhibited and prolonged survival time of LLC C57BL/6 mice was recorded. These findings suggested that *Bifidobacterium infantis*-mediated sFlt-1 gene transferring system presented a promising therapeutic approach for the treatment of lung cancer (Zhu et al., 2011).

In addition, a survey was conducted at the outpatient department of the National Cancer Institute in Slovakia about probiotic use and the association with patient tumor characteristics in cancer patients treated. The evaluation was performed by questionnaire form, including the length and method of use relative to anticancer therapy, expectations, side-effect experiences, understanding of the possible risks, dietary supplement use, and others regarding their overall experience with probiotics. Results showed that out of 499 different cancer patients used in the survey, 25 cases were of lung cancer only. The results showed that 60% (15) patients have found to be negative for the use of probiotics, whereas rest 40% (10) has given positive response (Ciernikova et al., 2017).

## 3. Indirect impact of probiotics in treatment of lung cancer

### 3.1. Probiotics preventing respiratory related diseases

With strong belief, it is now reported that probiotic treatment can decrease the severity of various infections in humans (Amara & Shibl, 2015). Over the past few years, several clinical trials have been performed via oral administration of probiotics, for reducing the incidence of various respiratory diseases (Marranzino, Villena, Salva, & Alvarez, 2012; Nagalingam, Cope, & Lynch, 2013; Villena et al., 2012). It has been reported that some probiotic bacterial species, like *Lactobacillus* and *Bifidobacterium*, can reduce the pathogen load in the respiratory system. This protective mechanism is supposed to be linked with the increasing working action of immune cells, such as natural killer (NK) cells and macrophages (alveolar system) (Hardy, Harris, Lyon, Beal, & Foey, 2013). In a previous study, two *L. rhamnosus* strains, CRL1501 (Lr05) and CRL 1506 (Lr06), were evaluated for resistance to *Salmonella typhimurium* an intestinal pathogen, and *Streptococcus pneumoniae*, a respiratory pathogen. With both strains, resistance against the intestinal pathogen was improved, but for lung infection, only one strain (Lr05) was able to decrease the number of cells, by inducing an increase in IFN-γ (Th1) and IL-4, IL-6, and IL-10 (Th2) cytokine levels in the Broncho alveolar lavage (Salva, Villena, & Alvarez, 2010).

As for lung cancer, smoking was also responsible for causing chronic obstructive pulmonary disease (COPD), which is the world's fourth largest killer (Mortaz et al., 2013). It appears that each of the subtypes of lung cancer is linked to COPD (Houghton, 2013). Therefore, these two diseases are linked, with the presence of COPD increasing the incidence of lung cancer and lung cancer death (Houghton, 2013). Recent studies have also established a role of miRNA as a pathogenic link between COPD and lung cancer (Shin & Brusselle, 2014). Cigarette smoking leads to impaired human NK cell cytotoxic activity and cytokine release (Aziz & Bonavida, 2016). In contrast to this, non-smokers have been reported to have higher NK cell activity (Morimoto, Takeshita, Nanno, Tokudome, & Nakayama, 2005). It has also been stated that NK cell activity can be enhanced by administration of LcS probiotic strains on a regular basis (Naruszewicz, Johansson, Zapolska-Downar, & Bukowska, 2002). Therefore, by intake of regular potential probiotic strains, the occurrence of lung cancer can be prevented. The detailed mechanism of NK cells has been described in the later section of the manuscript. Moreover, it has been reported that activation of lung cancer and COPD share various common pathways (Durham & Adcock, 2015; Guillemard, Tanguy, Flavigny, de la Motte, & Schrezenmeir, 2010). The probiotics may be useful in COPD patients, particularly those with frequent viral infections as they increase the function of NK cells along with mediators considered important in regulating the inflammatory response that occurs during COPD exacerbations (Mortaz et al., 2013). Therefore, it is possible that if these two diseases are closely related on a molecular level, then anti-inflammatory approaches using probiotics for COPD could also be beneficial for lung cancer prevention and treatment. Furthermore, recent studies have reported that IL-17 plays an important role in lung cancer and smoking is associated with polymorphisms in the IL-17 gene. It was studied that the frequency of lung cancer was significantly lower in IL-17 knockout mice with a lung-specific K-ras mutation than in mice with a local pulmonary K-ras mutation (Chang et al., 2014). Therefore, IL-17 is considered an important marker for the diagnosis and prognosis of lung cancer (Wu et al., 2016). In support one recent study established that a novel probiotic mixture has resulted in the reduction in the tumor growth due to down-regulation of IL-17 and its major producer cells (Li et al., 2016).

Asthma is one of the most common diseases of childhood, characterized by chronic inflammation of the lungs, presenting with airway hyper-reactivity, excessive mucous formation, and respiratory obstruction. Earlier, it was suggested that chronic inflammation-induced production of reactive oxygen/nitrogen species in the lung may predispose individuals to lung cancer (Azad, Rojanasakul, & Vallyathan, 2008). Recently a reported was published in reputed journal about the meta-analysis of the association between lung cancer and asthma, which suggested that asthma might be significantly associated with lung cancer risk (Qu et al., 2017). Probiotics such as lactobacilli and bifidobacteria have been reported to decrease asthmatic symptoms (Julia, Macia, & Dombrowicz, 2015; Wang et al., 2017). These probiotics confer benefits by helping T regulatory (Treg) cell development and rebalancing Th1/Th2 responses toward a Th1-dominant state (Kim, Lee, et al., 2014; Kim, Kim, et al., 2014). In support of this one research demonstrated that mice (BALB/c) sensitive to ovalbumin (OVA) were

orally administered with 6 different probiotic strains: *Bifidobacterium breve* M-16V, *Bifidobacterium infantis* NumRes251, *B. animalis* NumRes252 and NumRes253, *L. plantarum* NumRes8, and *L. rhamnosus* NumRes6. After OVA inhalation, their reaction to methacholine was measured and pulmonary inflammation was evaluated by analyzing the bronchoalveolar lavage fluid (BALF) for the presence of inflammatory cells and mediators. Out of 6 strains, mice administrated with the 2 strains, *B. breve* M-16V and *L. plantarum* NumRes8, showed some effects, like the reduced number of eosinophils in BALF, response to methacholine, and reduced levels of both OVA-specific IgE and IgG1. In addition, *B. breve* M-16V reduced interleukin IL-4, IL-5, and IL-10 levels, while *L. plantarum* NumRes8 reduced allergic skin reactions to OVA. The other strains, however, did not have any effect on the above-discussed parameters (Hougee et al., 2010). Another study demonstrated that *Lactobacillus gasseri* can suppress Th17 pro-inflammatory response and inhibit OVA- induced airway inflammation in mice (Jan et al., 2012). Recently, one study investigated the use of *Lactobacillus paracasei* L9 as a potential therapeutic agent to prevent or alleviate the particulate matter 2.5 (PM2.5) enhanced pre-existing asthma in mice (Wang et al., 2017). In this study, a mouse model of asthma (a 21-day ovalbumin (OVA) sensitization and challenge model) followed by PM2.5 exposures was used. Asthmatic mice were orally administered with L9 ($4 \times 10^7$, $4 \times 10^9$ CFU/mouse, day). The result indicated that the probiotic strain L9 may exert the anti-allergic benefit, possibly through rebalancing Th1/Th2 immune response and modulating IL-17 pro-inflammatory immune response (Wang et al., 2017). These results suggest that probiotics can play important role in the prevention of asthma associated lung cancer risk.

### 3.2. Impact on NK cells in host immune system

Modulation of host immunity is an important potential mechanism by which probiotics confer health benefits. An extensive literature has reported that the body's anomalous immune response can be prevented or treated with administration of beneficial probiotic bacterial strains (Konieczna, Akdis, Quigley, Shanahan, & O'Mahony, 2012). Experimentally, it was established that probiotics exhibit anti-cancer activity and have immunomodulatory effects on cancer cells via natural killer (NK) cells, macrophages, T cells, increased production of cytokines, antioxidants, and anti-angiogenic factors and reduction in cancer specific proteins and pro carcinogenic enzymes (Dasari et al., 2016) (Fig. 2). It has been reported earlier that NKG2D is the main activator receptor of NK cells, which is involved in NKG2D- NKG2D ligand (expressed over the surface of tumor cells) signaling pathway. This is responsible for induction of anti-tumor effects (Bae, Hwang, & Lee, 2012). One recent study has demonstrated that NKG2D ligands were also expressed on the surface of lung cancer cell lines (Yin et al., 2017). They have also investigated that NKG2D-NKG2D ligand interaction serves an essential role in mediating lung cancer cell (A549) killing *in vitro* by (cytokine-induced killer cells) CIK cells. These CIK cells are heterogeneous cells consisted of NK cells and certain T cells (Spear, Wu, Sentman, & Sentman, 2013). Previous research has confirmed that when mice were fed with the probiotic bacterial strain, *L. pentosus* S-PT84, NK cell activity increases, ultimately leading to production of IFN-λ. Increased IFN-λ production was due to IL-12 produced by CD11c1 dendritic cells (DCs) after a Toll-like receptor (TLR) 2- and/or TLR4-dependent interaction between the DCs and the bacteria (Koizumi et al., 2008). In another study, two *Lactobacillus* strains, *L. salivarius* and *L. fermentum*, were shown to increase both natural and acquired immune responses, as confirmed by activation of NK cells and expansion of regulatory T cells (Perez-Cano, Dong, & Yaqoob, 2010). In addition, the mechanism through which probiotics exert their anticancer functions (modulation of the inflammatory response, helper T cells and interferon γ level) were described in detail in a recent review (So, Wan, & El-Nezami, 2017). The increased immune functions by administration of probiotics would be helpful for the lung cancer prevention.

### 3.3. Effect of probiotics on lung immunity

The human body is prone to exposure to naturally available or industrially produced toxic chemicals (Singh & Kathiresan, 2014). Chemical carcinogens specifically affect various metabolic pathways as they interfere with genome integrity (Jang, Cotterchio, Borgida, Gallinger, & Cleary, 2012). Benzopyrene, one of the best examples of mutagens in the air, responsible for lung cancer (Ahmed et al., 2013). It has been reported that cell suspensions of different species of *Bifidobacterium* against benzopyrene show higher antimutagenic activities than their supernatants (Lo, Yu, Chou, & Tsai, 2002). Similarly, the effect of probiotic bacteria against two mutagenic substances, benzo [a] pyrene and sodium azide, was checked during different growth phases. The extracellular bioactive compounds from *B. adolecenti* ATCC 15,703 and *L. plantarum* ATCC 8014 have shown inhibitory effects on selected mutagenic substances (Chalvo, Lingbeck, Kwon, & Ricke, 2008). In addition, many entry routes of toxic heavy metals in the human body were reported. From an ecological point of view, the entry of heavy metals has been increasing with food chain contamination, making an indirect entry into humans through edible food or water sources (Nordberg, Nogawa, Nordberg, & Friberg, 2011). Previous research has established a link between lung cancer and heavy metal [arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), mercury (Hg), nickel (Ni), lead (Pb), and zinc (Zn)] contamination (Huang et al., 2013). Among these metals, Cd is classified as a group I human carcinogen by the International Agency for Research on Cancer (IARC, 1993). It has been reported that the genus *Lactobacillus* has the capacity to bind and detoxify some of these toxic substances (Monachese, Burton, & Reid, 2012). It was also reported that *B. longum*, *L. rhamnosus*, and *L. plantarum* were capable of binding heavy metals *in vitro* (Halttunen, Collado, El-Nezami, Meriluoto, & Salminen, 2008; Halttunen, Salminen, & Tahvonen, 2007). Thus, it can be hypothesized that if the appropriate combination of probiotic strains would be taken by people, the risk of onset of lung cancer can be reduced due to a reduction in the entry and continues removal of heavy metals from the body. Or else, continuous administration of probiotic bacteria could also be a preventive measure to save the human body from heavy metal poisoning, which is one of the major causes of lung cancer. In support of this, a study has been reported which used several probiotic bacterial strains for decontamination of food and water from heavy metals, toxins and pathogens (Zoghi, Khosravi-Darani, & Sohrabvandi, 2014). In addition, it is to be added here that wholesome (fruits, vitamins, vegetables, dairy products, meat and nuts) diet should be taken by the patients in addition to therapies and other treatments and evidences speak that these foods can be beneficial for the cancer patient's survival and possibly can prevent recurrence or the metastasis also (Bazzan, Newberg, Cho, & Monti, 2013). One study has reviewed that the pyridoxine stimulates anticancer immunosurveillance in the context of cisplatin-based chemotherapy against non-small-cell lung cancer (Aranda et al., 2015; Galluzzi et al., 2012). Therefore, it may be exciting to discover the therapeutic use of probiotics that produce pyridoxine (Commichau et al., 2015).

## 4. Conclusion and future prospects

Biotherapeutics represent a novel approach to treat lung cancer and offer extended benefits even in the treatment of respiratory diseases. The beneficial effects of these microorganisms are mainly via immunomodulation of gut microbiota. An improvement in the understanding of interaction between the immune system and probiotics will give insights into the development of probiotic-based therapeutics. Although clinical studies have demonstrated positive and encouraging results, more research is needed to identify potential strains, determine clearly the reaction mechanisms, and evaluate the effects of probiotic in order to harness the complete benefits. Extensive human clinical trials are required for specific types and stages of lung cancer. We believe that

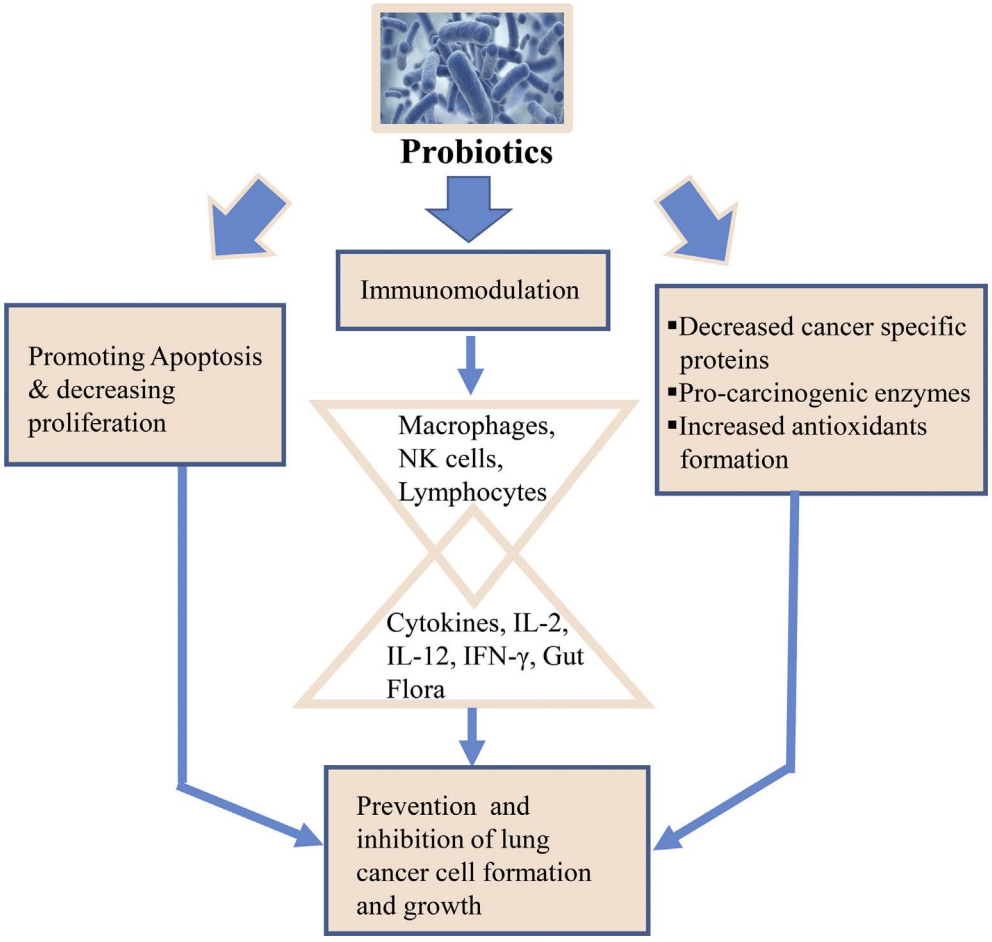


**Fig. 2.** Schematic illustration of effect of probiotics on host immune system. In response to probiotic bacterial strains, an increase in the activity of immune cells, antioxidants and cytokines leads to apoptosis of cancerous cells and decrease in the production of lung cancer specific enzymes and pro-carcinogenic enzymes which direct to the inhibition of lung cancer formation and growth.

different probiotic bacterial strain with other immunotherapeutic agents or different forms of treatment can be acknowledged as alternative therapy for lung cancer prevention or control. In parallel, as mentioned in previous literature, engineered probiotics can also be designed with specific properties and used for the prevention and treatment of lung cancer.

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## Conflicts of interest

There are no conflicts of interests.

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