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PREBIOTICS AND PROBIOTICS: A FOCUSED REVIEW OF APPLICATIONS IN RESPIRATORY DISORDERS

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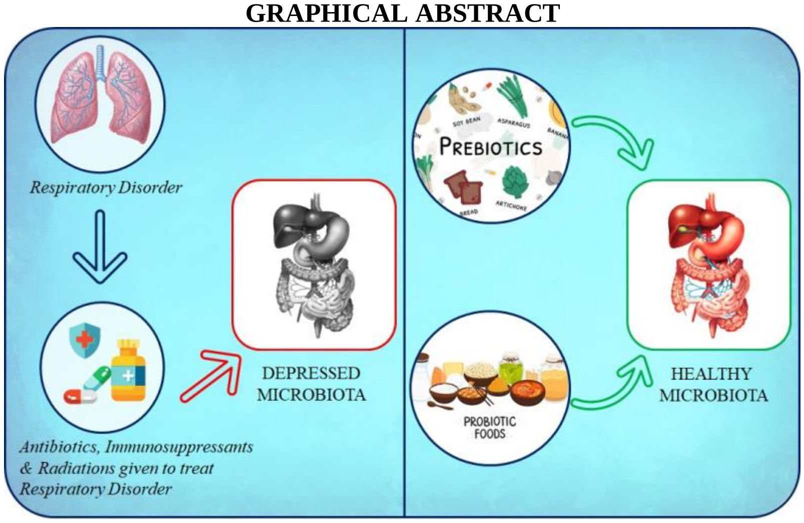
ABSTRACT

The principal function of food is to provide sufficient nutrients to achieve healthy diets and give a sense of fulfillment and health to people. The prevalence, seriousness, predicted patterns and economic effects of chronic respiratory conditions such as asthma, COPD, COVID-19, and other such diseases pose a serious public health challenge. The use of, among many other therapies, antibiotics, immunosuppressants, and radiation can induce alterations and influence the gastrointestinal biome. Therefore, it would be a very enticing choice to re-establish microbial balance and avoid disease if favorable microorganisms are introduced in the GIT. Probiotic and prebiotic ingredients have been the focus of substantial studies in recent decades in human nutrition with therapeutic potentials. The number of studies on possible health advantages that come via the use of probiotics and prebiotics has improved dramatically in the last few years. The concept of probiotic products has emerged from a live active culture that enhances the balance of the intestinal microbiota composition and the immunomodulatory capacity of clearly specified strains, to specific results. Prebiotics are short-chain carbohydrates that beneficially alter the composition or metabolism of intestinal microbiota. Therefore, prebiotics is supposed to improve wellness like probiotics but at the same time are economic, less toxic, and easier to introduce into the diet than probiotics. These are used to prevent and cure different medical problems and to encourage general well-being.

GRAPHICAL ABSTRACT



1.Introduction

Health statements about living microbes particularly lactic acid bacteria in food have a rich history. In an old-tape Persian version, it says that "Abraham owed the consumption of sour milk to his longevity." In 76 BC, the Roman historian Plinius suggested that gastroenteritis be treated with fermented dairy products (Schrezenmeir & De Vrese, 2001). Epidemiological studies suggest that food has an important effect on human wellness: diets with low fat and high fruit and vegetables have been associated with a reduced prevalence of certain ailments, including cardiovascular disease (CVD) and colorectal carcinoma. Such a diet involves not only components readily ingested in the small intestine but also digestion-free ingredients by the pancreas and small intestine enzymes (Blaut, 2002). It is only in the last 40 years that diets have played an important role in emerging illnesses such as CVDs and tumors. In this sense, among the most metabolically active parts of the human body is the colon which has a rather diverse microbial environment, which is not only a barrier to infection but also effectively contributes to the energy conservation from diets which cannot be influenced by enzymes of the human body (Kolida & Gibson, 2011).

The major cause of mortality and morbidity is airway diseases which affect the lives of more than a billion individuals worldwide. Chronic respiratory diseases (CRDs) are a broad type of major disease that is associated with the anatomy of the respiratory system. CRDs are regarded as a primary cause of accidental mortality in the world's population (KUMARI et al., 2020). Over time, the morbidity and mortality of CRDs are growing for infants and young children who are highly sensitive (Burney et al., 2015). Millions are dying owing to the inadequacy of healthcare without accessibility to immunizations (Ferkol & Schraufnagel, 2014). The responsibility of CRD and diagnosis messes up the frameworks of patients' daily lives and reduces activities (Dobler, 2019). CRDs include chronic obstructive pulmonary disorder (COPD), asthma, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), carcinoma of the lung, etc. COPD and asthma are the most prevalent of all these disorders with a very high degree of incidence and death. COPD is one of the leading international and Indian non-communicable causes of death (Salvi et al., 2018). More than 4 million deaths per year and 4% of the global prevalence of infectious diseases are CRDs (Wang et al., 2016). CRD risk factors are frequent and widespread: at least 2 billion people are vulnerable to the harmful effects of the use of biomass fuels, 1 billion to outdoor air emissions, and 1 billion smokers are exposed to the detrimental effects of second-hand smoking in a quasi-equivalent proportion in the population. Although CRDs are not curable, different types of treatment can help manage symptoms, improve the quality of life of patients and prevent adverse effects that are associated with severe morbidity, impairment, and risk of death (Soriano et al., 2020).

The use of, among other forms of treatment, antibiotics, immunosuppressive therapy, and radiation will induce alterations in the flora and composition. Thus, it may be very tempting to preserve microbial balance and avoid disease by adding beneficial bacterial organisms into the GI tract (Gupta & Garg, 2009). Probiotics have been identified in different ways according to our understanding of their pathways for effect on human well-being. Lilly and Stillwell coined the term probiotic to describe the substances developed by one microorganism which stimulate another's development (Salminen et al., 1999). These are live microbes that support the wellbeing of the individual if given in sufficient quantity. Many bacteria are used for a variety of applications in clinical practice. The most widespread and extensively studied species are *Lactobacillus, Bifidobacterium*, and *Saccharomyces* (Benjamin Kligler & Andreas Cohrssen, 2008).

First, a prebiotic was described as a "non-digestible food component that has a positive effect on the host by selectively stimulating bacterial growth and/or operation in the colon and thereby improving the health of the host (Ringø et al., 2010; Roberfroid, 2007). Some recognized prebiotics are low-digestible carbohydrates and have impaired gastrointestinal (GI) resistance, particularly in large amounts when consumed while other prebiotic fibres (e.g., wheat dextrin, polydextrose) show high GI resilience (Slavin, 2013). Though there is many prebiotics available in the world market, not all of these have been extensively studied, and thus, the scope for discovering new prebiotics is very much intrinsic. These can possess desirable attributes that are not present in the current generation (Rastall & Maitin, 2002).

Synbiotics have both probiotic and prebiotic features and have been developed to address the potential survival problems in the GI tract. A supreme impact can therefore, in contrast to the behavior of probiotic or prebiotic alone, be assured by the optimum combination of both components in one product (Markowiak & Ślizewska, 2017). Different health benefits of both pro- and prebiotics are shown in figure 1.

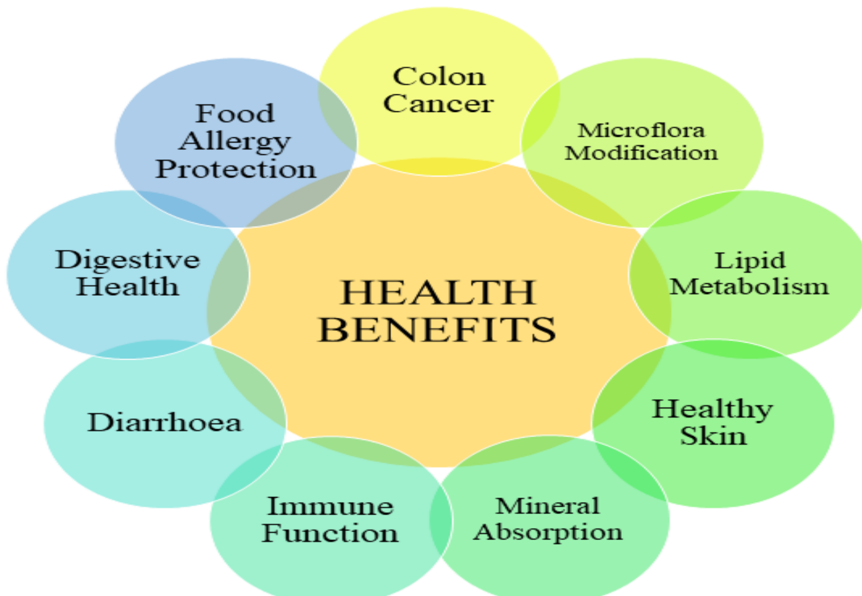


Figure 1. The health benefits of probiotics and prebiotics

2. Probiotics

In 1989, R Fuller popularised the term probiotics, which was defined as 'living micro-organisms that exert health benefits beyond general nutrition when ingested in certain numbers (Arthur C Ouwehand et al., 2002). These bacteria, normally non-motile and of different shapes, are fermentative anaerobic microbes. They generate lactic acid typically. Their biological characteristics allow them to predominate and prevail in the human digestive tract over potentially pathogenic microorganisms. It is currently speculated that these organisms produce low molecular metabolic by-products, including short-chain fatty acids such as butyrate, which have a favorable regulatory influence on host metabolic processes. Sometimes, these metabolic by-products are called "postbiotics" and can biologically function as immune modulators (Dan W Thomas & Frank R Greer, 2010). The terminology is drawn from early experiments that examine the influence on the overall structure of the human intestinal microbiota of some yogurt bacteria. Probiotics were first used for intestinal microbiota modification to affect both human and animal health. The basic ingredients of live microbial foods and their health impacts are currently researched in food matrices and as individual or mixed-cropped preparations (Isolauri et al., 2004).

Analysis and market interest in probiotics have risen dramatically in recent years. Increasing scientific data confirms certain of its medical benefits, notably when treating certain diarrheal disorders, associated with the use of probiotics. Yeast or bacteria consist of probiotics regulated as nutritional supplements and foods. They are sold as pills, tablets, packages, or powders, most commonly in yogurt or milk beverages. A single microorganism or a combination of several species can be included in probiotic products (Williams, 2010).

The rising numbers of modern illnesses, such as malignancies, atherosclerosis, heart attacks, high blood pressure, and HIV infection, have stimulated attention to probiotics. A multitude of beneficial effects have been documented in the probiotic intake, including improved immune reactions, controlled colonic microbiota effects, vaccine adjuvant effects, decreased fecal enzymes involved in initiating cancer, travel-related diarrhoea treatment and anti-biotic medication, rotavirus regulation, and the Clostridium difficile colitis and ulcer prevention associated with Helicobacter pylori (Kaur et al., 2002). The processes underlying the use of probiotics to exercise biological effects remain unclear, but the unidentified factors such as resistance to colonization and competition exclusion sometimes explain their method of action (Soccol et al., 2010). Table 1 enlists the known microbial species which are used as probiotics.

Table 1. List of micro-organisms used as Probiotics (Chow, 2002)

***Bifidobacterium* species**	***Lactobacillus* species**	***Saccharomyces* species**	***Streptococcus* species**	**Other species**
B. adolescentis *B. bifidum* *B. breve* *B. infantis* *B. lactis* *B. longum*	*L. acidophilus* *L. bulgaricus* *L. casei* *L. fermentum* *L. gasseri* *L. johnsonii*	*S. boulardii*	*S. thermophilus* *S. salivarius subsp. thermophilus*	*Bacillus cereus* *Bacillus subtilis* *Escherichia coli* *Enterococcus* *Propionibacterium freudenreichii*

3. Prebiotics

In 1995, Gibson and Roberfoid presented the idea of prebiotics as an effective solution to gut microbiota modulation (Charalampopoulos & Rastall, 2012). The FAO/WHO describes prebiotics as an unsustainable food element, which provides the host with health care benefits connected with microbiota modulation. Prebiotics are a community of complex, unidentified carbohydrate ingredients based on their source, fermentation characteristics, and dose about health benefits. Prebiotic sources include breast milk, soy, inulin, raw oats, unrefined wheat, unrefined barley, non-digestible carbs especially non-digestible oligosaccharides (Pandey et al., 2015). Currently, all the prebiotics are short-chain carbohydrates with a polymerization of between 2 and 60, which are known to be non-digestible with human or animal digestive enzymes (Cummings J.H.* & Macfarlane, 2002). The importance of prebiotics is due to:

a. the growing belief that a stable or healthy intestinal microbiota exists
b. the indication that the microbiota makeup may be altered by prebiotics toward a healthier profile
c. An alternate to probiotics difficult to control in certain foodstuffs, but whose health benefits are increasingly well known as regards the prevention of diarrhoea and immunomodulation

d. Since currently used prebiotics, particularly inulin and galactooligosaccharides (GOS) are fairly inexpensive to produce and collect from crops and have beneficial effects on the gut microbiota and host, these are also useful functional components in foods with the potential to enhance organoleptic propagation on fat and dairy products (Macfarlane et al., 2006).

When taken in comparatively small quantities (5-20 g/day) of the inulin, fructooligosaccharides (FOS), trans-GOSs, and lactulose, the development of organisms (responsible for health promotion) belonging to the genera Bifidobacterium and lactobacillus in human beings was clearly shown in the studies (Gibson et al., 2004).

Prebiotics travel into the small intestine and become available without the need for other intestinal bacteria for probiotic bacteria. The frequently used prebiotics in human diets is lactulose, GOS, FOS, inulin and hydrolysates, malto-oligosaccharides, and resistant starch. A prebiotic for one or a small quantity of probiotics is the selective substratum. Probiotics are allowed to develop and produce short prebiotic chain fatty acids. The Prebiotic will then shift the host's colonic microbiota to a healthy condition (Al-Sheraji et al., 2013). Table 2 details the various types and sources of prebiotics.

Table 2. Types and sources of prebiotics (Al-Sheraji et al., 2013).

Type	**Sources**
Arabinoxylo oligosaccharides	Wheat bran
Cyclodextrins	Water-soluble glucans
Fructo oligosaccharides	Asparagus, sugar beet, garlic, chicory, onion, Jerusalem artichoke, wheat, honey, banana, barley, tomato, and rye
Galacto oligosaccharides	Human’s milk and cow’s milk
Isomaltulose	Sucrose
Isomalto oligosaccharides	Starch
Soybean oligosaccharide	Soybean

4. Common Diseases

a. Asthma

Asthma is one of the most prominent non-communicable disorders which has a serious influence on the living quality of many people. About 300 million people worldwide have asthma, and another 100 million are expected to be affected by 2025 (Dharmage et al., 2019). Asthma is a chronic inflammatory disorder of the respiratory tract in which many of the cells in the adaptive and innate immune systems work alongside the cells of the epithelium to create bronchial hyperreactivity (BHR), excess production of mucus, remodeling of the respiratory wall, and narrowing of the respiratory tract. This contributes to repeated breathing problems, wheezing, and tightness of the chest in vulnerable patients (Lambrecht & Hammad, 2015). These symptoms temporarily fluctuate and may intensify during times of exacerbation resulting in respiratory failure (Lambrecht et al., 2019). The most critical symptom in the detection of asthma is wheezing (Ferrante & La Grutta, 2018), however, there may be separate cases for the relative severity, type of inflammatory cell, and location of inflammatory infiltrate. A significant number of cells participate in the immune and inflammatory reactions to asthma allergens including T-cells, eosinophils, mast, and neutrophils (Hamid & Tulic, 2009). Effective management and care of asthmatic patients can eliminate the mortality of the disease, while one in 250 attributes to the global mortality of asthma (P. Kumar & Ram, 2017). Amid the progress made in asthma care throughout the past few decades, changes in patient preparation, the use of innovative medical methods, and personalized support services have yet to be completed.

b. Chronic Pulmonary obstructive disease (COPD)

Because of its higher incidence and resulting impairment and death, COPD is a major public health problem. Worldwide, the third leading cause of death is COPD; 3.2 million deaths were reported in 2017, and a total of 4.4 million per year is expected by 2040 (Bartolomé R. Celli & Wedzicha, 2019). The disease has been generally recognized as an illness caused by cigarette smoke. The classic idea was to develop an irregular inflammatory reaction in vulnerable people to destroy the airways and alveoli (emphysema), speed up the physiologic drop in lung capacity with age, and reduce breathing limitation and CR symptoms (Agustí & Hogg, 2019). Patients with COPD have a distinct inflammatory pattern- the more usually type 1 immunity and type 3 immunity-predominantly macrophages and neutrophils with elevated CD8+ cytotoxic T cell levels, CD4+ TH1 cell, TH17 cell, ILC3, and B cells, and are grouped in peripheral airways with T cells in local lymphatic follicles (Barnes, 2018).

c. Covid-19

A current coronavirus (CoV), known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has developed an on-going global threat, reported by international health agencies (Malik et al., 2020; Mohit & Hussain, 2021). The sudden onset and rapid spread of the infection have led to an outbreak. The root of the virus is suspected in numerous animals eaten as food in China, but not been proven. The initial infection research revealed that there is a correlation between both the local and wild animal markets in China with most of the early infections. Subsequently, new infections are often transmitted through transmission from human to human (Chhikara et al., 2020). However, research suggests that asymptomatic patients also can spread the virus through droplets in the air produced while sneezing or coughing (Agarwal et al., 2020). About 26-32 kilobases in size, the most commonly recognized RNA virus, are enveloped by CoV of the Coronaviridae family (CoVs) with a single strand, RNA-positive sense genome. The term 'coronavirus' refers to the presence of the CoV virus when viewed under an electron microscope, which gives the appearance of a crown or a corona in Latin to spike projections from the virus membrane (Su et al., 2016). COVID-19 covers a wide variety of symptoms, from high respiratory problems to dangerous pneumonia associated with acute respiratory distress syndrome (ARDS). Fever, weakness, dry cough, myalgia, and dyspnea are the most common symptoms displayed. Patients with headache, hemoptysis, diarrhea, or pleuritic of the chest are less often seen. At present, in the case of upper and lower respiratory track specimens, a reference procedure for diagnosing COVID-19 is a real-time reverse transcriptase polymerase chain reaction (RT-PCR) (Jajodia et al., 2020). Globally, the CoV incubation period is 3-7 days. About 80% of infectious cases persist as mild or asymptomatic, 15% are severe, and 5% are critical, with a requirement for ventilation (Hussain et al., 2021).

d. Lung Cancer

Lung carcinoma has evolved in the last century, from a rare, dim disease to the world's most advanced carcinoma and the most widespread cause of tumor mortality. The identified lung cancer risk factors include behavioral, environmental, and genetic factors, all of which have a role in the growth of the disease and also influence the response capability of particular patients (de Groot et al., 2018). The second-most prominent gender-based carcinoma diagnosis behind prostate cancer in men and women's breast cancer is lung carcinoma. In 2018, lung carcinoma accounted for 14 percent of new male and 13 percent of new female cancers in the United States (Siegel et al., 2018). Per year, lung cancer affects 1.8 million people and the illness causes 1.6 million deaths. Five-year survival of lung cancer populations ranges from 4% to 17%, based on stage and geographic variations (Hirsch et al., 2017). The risk of developing lung carcinoma in smokers is 20-30 times significantly greater than in those who do not smoke. Lung carcinoma rates are rising parallel to tobacco use in developing nations. Future preventive measures and research can focus on and clarify state-of-the-art exposures including non-cigarette products to modifiable non-tobacco factors. The 2004-2008 data for Surveillance, Epidemiology, and End Result (SEER) indicated that lung carcinoma has been detected at a median age of 71 years (S & Hussain MS, 2021).

5. Mechanisms of Action of Probiotics in Various Diseases

a. Immunomodulation

Various studies conducted on animals and humans reported findings that variant strains of lactic acid bacteria (LAB) can induce and manage natural and adaptive immune responses. Bifidobacteria and lactobacilli strains were found to have distinctive capabilities to adjust and regulate immune responses (H. Gill & Prasad, 2008). The mechanism of action of probiotics is not completely known. The immune reaction towards the probiotics depends upon the variant and distinction because of the availability of disparate presence of protein/carbohydrate in the cellular walls (Mortaz et al., 2013). The advantageous effectiveness of probiotics is partially a consequence of the capability of probiotics, to modulate the formation of anti- and proinflammatory cytokines as well as the equilibrium between kinds of T-cell responses like T-helper 1 (Th1), Th2, and, Th17 (Ghadimi et al., 2008; Helwig et al., 2006; Hosono et al., 1986). Cytokines are one of the greatest mediators showing their role in inflammation and immunity responses. Cytokines mediate the beginning, sustenance as well as resolution of the natural and adaptive immune response. Various studies have shown that probiotics increase levels of interferon-γ (IFN-γ), IFN-α and interleukin-2 (IL-2) in individuals administered with probiotics (Halpern et al., 1991; Kishi et al., 1996; Solis Pereyra & Lemonnier, 1993; Wheeler et al., 1997). Regular intake of yogurt also leads to the elevated formation of IL-1β, IL-6, IL-10, tumor necrosis factor (TNF-α), and IFN-γ (Aattouri & Lemonnier, 1997; Halpern et al., 1991; Miettinen et al., 1996; Solis Pereyra & Lemonnier, 1993). This stimulation of cytokines and interferons in epithelial and dendritic cells (DCs) acts as a key way to tackle viral infections by removing viruses through the mediation via cell-to-cell and also the adaptive immunity (Lehtoranta et al., 2014). As per a randomized control trial, when the various probiotic strains were given to serious sepsis-suffering children, it was reported that proinflammatory cytokines such as IL6, and TNF-α were diminished and anti-inflammatory cytokines such as IL-10 levels were elevated in comparison to those who received placebo (Suresh K. Angurana et al., 2018). LAB when given by oral route not only adjusts and regulates the cytokines in the intestinal region but also at the systemic level (Noverr & Huffnagle, 2005). Immunity responses are elevated by various LAB variant strains to constitute the proliferation of T-lymphocyte and antitumor capability of natural killer cells (NK) as well as the phagocytic activity of mononuclear cells (Harata et al., 2009). Phagocytic cells are efficacious in removing pathogenic microbes and NK cells are important for safe guarding against cancer cells as well as different viruses. Several studies have revealed the capability of probiotics to enhance the phagocytic actions of leucocytes (Harsharnjit S. Gill, 2003). As per a recent hypothesis, probiotic bacteria such as LAB can interact with Gut-associated lymphoid tissue which is present in payer's patches in the gut and can increase respiratory immunity and probiotics need not be directly given in the airway for airway-related diseases (Izumo et al., 2010). For natural immune receptors for instance toll-like receptors (TLRs) which are generally executed on epithelial cells as well as immune cells of mucosa, probiotics generally act as ligands to affect different signal paths consisting of nuclear transcription factor nuclear factor-kappa B (NF-kB) as well as peroxisome proliferator-activated receptor-γ (PPAR-γ) (Bermudez-Brito et al., 2012; Thomas & Versalovic, 2010). According to a study conducted on new born rats, it was shown that L. reuteri DSM 17938 considerably elevated the survival and lessen the occurrence and seriousness of experimental Necrotizing enterocolitis (NEC) in rat intestine by restriction of TLR4 and NF-kB signal path. These actions of probiotics lead to declined formation of TNF-α and IL-1β (Y. Liu et al., 2012). Increment in the NK activity and escalation in overall percentage of NK cells by routine taking of probiotic food like yogurt and curd was showed in various studies (Chiang et al., 2000; H. S. Gill et al., 2001; Olivares et al., 2006; Sheih et al., 2001). Cell interceded and antibody intervened responses are involved in adaptive immune responses and it is quite particular in action and has memory. Intake of some particular probiotics reported to increase antibody reactions and also local and systemic immunizations (Fukushima et al., 1998; Isolauri et al., 1995; Kaila et al., 1992; Link-Amster et al., 1994; Majamaa et al., 1995). According to a randomized study conducted by Kaila *et al.*, greater levels of particular serum and mucosa antibody reactions in children infected with rotavirus administered with L. rhamnosus GG fermented milk were observed when compared to children administered with only placebo (Kaila et al., 1992). In those cases, with salmonella vaccination, where probiotics such as B. bifidum were administered, considerably greater levels of particular serum immunoglobulin A (IgA) and IgA secreting cell response were reported (Fang et al., 2000; Link-Amster et al., 1994).

b. Antiviral/Antimicrobial Effects of Probiotics

Primarily viruses bind to the host cell and then the disease progresses; thus, if this step is interrupted, it may lead to a decline in disease progression and can be advantageous to the host. Probiotics may precisely bind to viruses and restrict them from binding with host cells. For example, particular variants of LAB have been found to inhibit the attachment of flu-like stomatitis virus in in-vitro conditions (Botić et al., 2007). Anti-microbial activities are reported to be shown by probiotics by forming various compounds such as bacteriocins, hydrogen peroxide, and various organic acids. In a study, metabolic intermediates of bacteria in the yogurt exhibited antiviral action against duplication of the influenza virus (Choi et al., 2009). In the case of the influenza virus, probiotics were found to modulate the immune responses and help in viral elimination as well as advantageous effects on inflammation caused by lung damage (Zelaya et al., 2016). In an in-vitro study conducted by Ang *et al*., comprising colon cells and skeletal muscle of humans, it was reported that L. reuteri exhibited considerable dose-dependable anti-viral action against enterovirus seventy-one strain and coxsackie virus type A (CA) six and sixteen strain (Ang et al., 2016). Commonly viruses may lead to upper respiratory tract infections. A Cochrane review of 12 randomized controlled trials found that in comparison to a placebo, probiotics were better at reducing acute upper respiratory tract infection (Hao et al., 2015). The flowchart (fig. 2) given below represents the mechanism of action of probiotics.

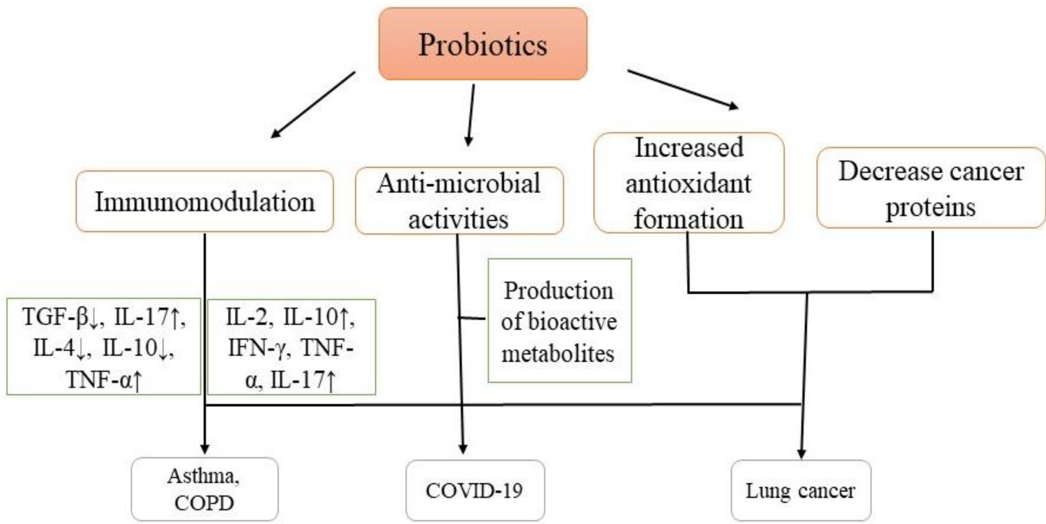


Figure 2. Mechanism of action of probiotics in respiratory disorders

c. Production of Bioactive Metabolites

Several bacteria present in the gut or particular probiotics have been shown to form various bioactive metabolites such as histamine, rheuterin, and butyrate with anti-inflammatory effects. L. reuteri variants obtained from humans form reuterin which has wide-spectrum antimicrobial activity against various intestinal microbes (Casas & Dobrogosz, 2000). Glycerol is broken down into smaller components by L. reuteri to form vitamin B12-reliant reuterin (Y. Liu et al., 2018). L. reuteri ATCC PTA6475 variant which is derived from humans, produces histamine which restrains inflammatory response, through activating type-2 receptor of histamine in intestinal parts of mammals, which leads to the restraining of inflammation of intestinal parts as well as colorectal tumorigenesis (Ganesh et al., 2018; Gao et al., 2017). Probiotics also can break down particular kinds of fibres to form short-chain fatty acids (SCFAs) like butyrate. SCFAs act as protection of host and have an important part in immune responses in addition to antioxidant action and activities against malignancy (Peng & Biswas, 2017). Butyrate intervenes inflammatory signal path to manage the formation of cytokines and also restricts the histamine deacetylase for adjusting the exhibition of several proinflammatory genes (Y. Liu et al., 2018).

6. Effects of Probiotics on Various Diseases

a. Asthma

The effectiveness of probiotics in the cure or prevention of asthma has been focused on by a few studies. A clinical trial was conducted on 1187 children by Giovannini *et al.* to study the efficacy of fermented milk consisting of L. casei on the occurrence of asthma and allergic rhinitis. It was observed that there was no distinction between the controlled and experiment groups in the case of asthma in 12 months of the trial (Giovannini et al., 2007). Another randomized controlled study of adults and juveniles reported that there was no betterment in signs in those who were administered with yogurt consisting of S. thermophilus and L. bulgaricus in the absence or presence of L. acidophilus and also there was no distinction in the inflammatory markings (Wheeler et al., 1997). In a double randomized, placebo-regulated study including toddlers with the possibility of allergy, it was reported that repetition of wheezing episodes was not reduced because of probiotic intake, and also it could not have any effect on the pervasiveness of asthma till two years of age

(Abrahamsson et al., 2007; Taylor et al., 2007). In another case, asthma-related signs were averted in toddlers with atopic dermatitis, and with the administration of probiotics, there was a considerable reduction in the expiration flow (Van Der Aa et al., 2011). In a mouse model, intake of probiotics via the oral route weakened the signs of allergic asthma, stimulated by the adjustment of immune responses by the regulatory T (Treg) mechanism, and reduced air passage hypersensitiveness (Jang et al., 2012). Several infections related to respiratory parts specifically viral infections precisely can cause comorbidities as well as can lead to fatality and asthma-like conditions also. It has been contemplated that if probiotics are recognized can prevent or manage virus infections, then in the initial years of life, asthma can be prevented (Holtzman et al., 2009; Yoo et al., 2007).

b. Chronic Pulmonary obstructive disease (COPD)

The most significant role is played by smoking as a lifestyle-associated factor in the development of COPD (Barnes, 2010). The seriousness of COPD in patients is related to the degree of inflammation in an air passage which is crucially associated with the pathogenesis of COPD in experimental conditions [100]-[102]. Characterizations such as escalated shortness of breath, increased phlegm, elevated inflammation, and a decrease in lung activity are seen in COPD (Bhowmik et al., 2000; Sapey & Stockley, 2006). The worsening of COPD symptoms is primarily because of viral infections in forty to sixty percent of cases (B. R. Celli & Barnes, 2007; Sapey & Stockley, 2006). In animal models, increased respiratory and enhanced airway apoptosis is caused by virus infection post-exposure to cigarette smoke (B. R. Celli & Barnes, 2007). Commonly it is acknowledged that, after virus infection, primary immunity response depends upon the detection of pathogen-associated molecular pattern molecules by TLRs such as TLR7 (Kang et al., 2008; Newman & Riley, 2007). These receptors are present in DCs and inflammation cells and induction of these causes stimulation of NK cells by forming IL-12, IL-15, etc. (Kawai & Akira, 2006; Lucas et al., 2007; Newman & Riley, 2007). In managing virus infections in primary phases, NK cell stimulation is crucial (Strowig et al., 2008). NK cells were considered just killer cells because of their capability to damage virus-affected cells (Ortaldo et al., 1991). Now consideration is also being given to the noncytotoxic effects of NK cells (Strowig et al., 2008). Stimulated NK cells form greater concentrations of IFN-γ (Schroder et al., 2004). IFN-γ stimulated by NK cells is crucial for the inflammation process that keeps virus infections in check (Orange et al., 1995; Scharton & Scott, 1993). NK cells and the mediators are thought to be crucial in COPD condition worsening symptoms. The use of cigarettes leads to hindered cytotoxic actions of NK cells and the generation of cytokines (Mian et al., 2008). Those individuals who do smoke have lesser activity of NK cells than those who do not smoke (Morimoto et al., 2005). Everyday routine administration of L. casei probiotics leads to enhanced NK cells (Naruszewicz et al., 2002). Thus, it is advised that probiotics can be beneficial in COPD-suffering individuals, especially those who have repetitive virus infections (Morimoto et al., 2005).

c. COVID-19

Lactobacillus and Bifidobacterium are probiotics that may act at various phases in the case of COVID-19 unlike antiviral drugs as well as drugs used to cope with inflammation which act in a few phases. Probiotics may play a role in the reclamation of the microbiome of the gut region, managing cytokine storm, averting other virus and fungus invasions as well as having antiviral activities (Suresh Kumar Angurana & Bansal, 2020). Such activities of probiotics can help in averting and/or improving the signs associated with COVID-19 and provides passive proof to use probiotics in the management of the novel coronavirus disease. Also, the probiotics are inexpensive, and effortlessly accessible and administration is not difficult in comparison to drugs utilized in COVID-19 against viruses (Infusino et al., 2020). When food ferments, bioactive peptides are formed by probiotics, and those compounds can restrict angiotensin-converting enzyme (ACE) by hindering the active sites. The litter of dead probiotic cells plays antagonizing role for the ACE enzyme (Olaimat et al., 2020). Probiotics can impede the ACE receptor which plays a role in access of severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) to host gastrointestinal cells. For this virus, no standard management regimes are available yet. The utilization of probiotics in managing COVID-19 has not been confirmed by any trials, but managing COVID-19 clinically can be an appropriate plan. Various trials are being conducted to access the efficacy of probiotics in curing COVID-19-suffering individuals (Infusino et al., 2020). Few individuals suffering from COVID-19 showed dysbacteriosis in the intestine represented by lesser probiotics such as lactobacillus etc., which suggests that those individuals may have feeble immunity thus, administration of probiotics can be beneficial to stabilize the imbalanced microflora and also in reducing the possibility of infection (Xu et al., 2020). Intake of probiotic foods such as fermented products can improve symptoms of COVID-19. According to research, the intake of fermented milk with probiotics may considerably decrease the occurrence of upper respiratory tract infections (Makino et al., 2010; Merenstein et al., 2010; Shida et al., 2017; Taipale et al., 2011). Because of the role of probiotics in several virus infections, it can be considered in COVID-19 management without concrete proof. It has been established with an escalation of age that there is a decline in gastrointestinal microflora and its variation also reduces. This reduction is a cause of various ailments in elderly people such as diseases linked to inflammation, obesity, etc. Individuals with imbalanced microbial flora and old aged people are more prone to be infected with COVID-19. Thus, in such cases, probiotics can act beneficial and help strengthen immunity by helping the intestinal microflora to modulate the immune responses (Olaimat et al., 2020).

d. Lung cancer

Around the world, the occurrence of cancer and death rates have elevated over the previous 10 years, and probiotics act in safeguarding against several cancers and it spellbound the science society. Various findings have shown the utilization of probiotics in preventing and managing distinct kinds of cancers (M. Kumar et al., 2010). The attainable multiple health-related effects of probiotics can be antimicrobial, antitumor, retarding the development of a tumor and enhancing natural and acquired immunity, precise restriction of food-originated microbes by competing as well as help in alleviating adverse effects of chemotherapy (P. C. Liu et al., 2017; R. M. Patel & Denning, 2013; Raman et al., 2013).

7. Direct Effect of Probiotics on Lung Cancer

According to a study, if the flora of the intestine is in equilibrium then it acts as a safeguard in managing malignancy (Iida et al., 2013). The use of probiotics in lung cancer is being considered nowadays. In research including 30 lung cancer-suffering individuals, it was examined whether gut microbiome got enhanced or not upon treating with chemotherapy along with probiotic supplementation. The group in which chemotherapy and probiotics were given in a combined way was reported to have enhanced gut microbiome and declined intestine indigestion whereas, in the case of another group with only chemotherapy, the individuals reported to have constipation and decline in lactobacillus and Bacteroides and disease-causing bacterial strains were elevated (Serkova et al., 2013). Another study was conducted in-vivo on the lewis lung cancer (LLC) bearing mice to elaborate utilization of probiotics. Lung malignant cells were in 3 different groups, and it was found that groups with cisplatin as well as cisplatin/antibiotic combinations such as vancomycin, ampicillin, and neomycin, found to have lesser continuity rate than the group with cisplatin/probiotics (L. acidophilus). In this case (cisplatin/probiotics), the continuity rate of life was lengthier. Furthermore, the activity of probiotics on cancer-suppressing as well as oncogenes was also examined and it was found that the exhibition of oncogenes declined and the exhibition of cancer-suppressing genes was diminished (Gui et al., 2015). In another study on tumor cell lines such as lung carcinoma cell lines (SK-MES-1), breast adenocarcinoma (AGS), and colon carcinoma (HT-29), the actions of strain Lactococcus lactis KC24 were observed. Rapid multiplication of SK-MES-1, AGS, and HT-29 was restricted by 86.53 %, 90.12 %, and 68.30 % sequentially (Lee et al., 2015). A study on probiotic L. lactis NK34 showed that the strain showed anti-cancer activity as well as anti-inflammation properties against different carcinoma cell lines such as SK-MES-1, AGS, etc. As a consequence of managing with L. lactis, it led to firm inhibition of cell rapid multiplication; in the case of SK-MES-1, it was 96.71 % and for AGS it was 82.07 %. Because of its anti-inflammatory activity, L. lactis NK34 was found to have decreased proinflammation cytokines (Han et al., 2015). In a study conducted to evaluate the effectiveness of a vaccine with probiotics against cancer solid sarcoma 37 (S37) and lewis lung carcinoma, it was found that consolidation of vaccine and probiotic strains mixture of *Enterococcus faecium* and *Saccharomyces cerevisiae* 14 K led to a combined enhanced effect of vaccine and probiotics in treating the S37 in mice and lewis lung carcinoma. The consolidated effect was turned up by 2-2.5 in comparison to the vaccine alone (Tanasienko et al., 2005). In another study, in which fermented milk with L. casei CRL 431 was given to BALB/c mice and it was found that there was a restriction of cancer development, and reduced lung metastasis (Aragón et al., 2015). According to a study conducted to evaluate the effect of probiotic-containing fermented milk products on lung metastasis, fermented milk products showed, toxicity toward 4T1 breast tumor cells (Zamberi et al., 2016).

8. Mechanism of Action of Prebiotics

The assumed mode of action of prebiotics can be in distinct ways, such as direct and indirect approaches. In the case of an indirect approach, sustenance is provided to gut microflora by prebiotics which leads to natural development, thus, leading to health advantages. In direct mode, there can be precise restriction of various disease-causing bacteria, prohibition of malignancy, etc. (Al-Sheraji et al., 2013; S. Patel & Goyal, 2012).

9. Therapeutic Effects of Prebiotics

a. Effects against pathogens

Probable utilization of prebiotics in different animal studies has been shown, concerning gastric infections. Against several diseases causing bacteria such as *Escherichia coli* by the usage of different modes including the formation of restrictive factors such as bacteriocin, SCFA and elimination by competing, etc. (Emanuel Vamanu & Adrian Vamanu, 2010; Licht et al., 2012). Actions of prebiotics such as inulin, dahlia, raffinose, and lactulose on the formation of bacteriocins have been studied from L. paracasei CMGB16 variant. It was reported that on supplementing the medium with inulin, raffinose, and lactulose, there was a considerable elevation in the actions of bacteriocin (Emanuel Vamanu & Adrian Vamanu, 2010). Bacteriocin formation by Pediococcus acidilactici LAB 5 is effected positively by prebiotic sorbitol (Mandal et al., 2009). In prohibiting pathogens, SCFA has a key role in decreasing the pH of the gastrointestinal tract. Lowered pH leads to a decrease in the decomposition of peptides (Mohanty et al., 2018). Colonic crypt cells are induced by SCFA, which reduces the possibility of intestinal mutation and helps in elevating the biomass by escalating protein formation (Cavaglieri et al., 2003; Coles et al., 2005; Fooks & Gibson, 2006).

b. Activities against Cancer

Prebiotics play the guarding role against cancer-causing substances in case of colon cancer. Propionate is SCFA which has properties against inflammation in colon cancer cells. Galactooligosaccharide (GOS) fermentation forms butyrate which manages apoptosis and decreases the metastasis in colon cancer cells. It improves the exhibition of enzymes that causes detoxification leading to safeguarding from cancer-causing compounds (Nurmi et al., 2005; Pool-Zobel, 2005; Pool-Zobel & Sauer, 2007). Lists of patents in prebiotics and probiotics are shown in Table 3 (Dixit et al., 2016). Table 4 lists the Commercially available probiotics and prebiotics and their information regarding the manufacturer, source, and origin (Douglas & Sanders, 2008; Mishra et al., 2018)**.**

Table 3. Patents involved with different probiotics/prebiotics

Probiotics/Prebiotics	**Patent Involved**	**Inventors**
Bifidobacterium longum	EP2318513A1	Jens Kildsgaard, Thomas Dyrmann Leser, Thomas Gunnarsson, Mette Weise, Ditte Marie Folkenberg, Thomas Janzen, Benedicte Flambard
Lactobacillus plantarum	US20160151434A1	Young Kwack, Se Jin You, Tae-Hun Park, Bum Jin Lee, Kye Ho Shin, Jin Oh Chung, Jun Cheol Cho
Streptococcus sanguis	US20140023620A1	Natalya Ioudina
Bacillus coagulans	US8697055B2	Sean Farmer
Enterococcus faecium	US20070098744A1	Ruth Knorr, Christoph Cavadini, Jalil Benyacoub, Ebenezer Satyaraj
Oligosaccharide	US20120294980A1	Albertus Alard Van Dijk, Yulia M. Efimova, Margot Elisabeth Francoise Schooneveld-Bergmans, Natalja Alekseevna Cyplenkova

Table 4. Commercially available probiotics and prebiotics

Sources/ Strain	**Brand/ Trade name**	**Type**	**Manufacturer**	**Origin**
Lactobacillus casei Immunitas	Actimel	Probiotics	Danone	France
Short-chain fructooligosaccharides	Ensure Fiber	Prebiotics	Abbott Nutrition	United States
Lactobacillus reuteri	Rela	Probiotics	Ingman Foods	Finland
Oligofructose, inulin, or combination	Cereal bars, meal replacement	Prebiotics	South Beach Diet	United States

	bars, and snacks			
Bacillus sp. strain IP5832	Bactisubtil	Probiotics	Synthelabo	Belgium
Lactobacillus strain	Jovita Probiotisch	Probiotics	H & J Bruggen	Germany
isomaltooligosaccharides	VitaFiber	Prebiotics	BioNeutra	United States
Lactobacillus casei Shirota	Yakult	Probiotics	Yakult	Japan
Lactobacillus strain	Vifit	Probiotics	Campina	The Netherlands

10. Conclusions

Approximately 10^{14} bacterial cells can hold the human intestine which can impact individual wellbeing. The regulation of the microorganisms in the intestines by diets (e.g., pro- and prebiotics) can be seen as a wonderful opportunity to affect people's health favorably. However, with certain health arguments made for pre- and probiotics, there are no definitive proofs and there is no appropriate explanation for their mechanism of action to describe these results. To conclude, a mixture of fundamental and applied science is desperately required to test intensively the health arguments made for pro and prebiotics and to learn about the actual mechanistic approach. Well before final declarations on the importance of pro- and prebiotics can be made- several unanswered issues need to be addressed.

11.References

Aattouri, N., & Lemonnier, D. (1997). Production of interferon induced by Streptococcus thermophilus: Role of CD4+ and CD8+ lymphocytes. *Journal of Nutritional Biochemistry*, *8*(1), 25–31. https://doi.org/10.1016/S0955-2863(96)00147-7

Abrahamsson, T. R., Jakobsson, T., Böttcher, M. F., Fredrikson, M., Jenmalm, M. C., Björkstén, B., & Oldaeus, G. (2007). Probiotics in prevention of IgE-associated eczema: A double-blind, randomized, placebo-controlled trial. *Journal of Allergy and Clinical Immunology*, *119*(5), 1174–1180. https://doi.org/10.1016/j.jaci.2007.01.007

Agarwal, K. M., Mohapatra, S., Sharma, P., Sharma, S., Bhatia, D., & Mishra, A. (2020). Study and overview of the novel corona virus disease (COVID-19). *Sensors International*, *1*, 100037. https://doi.org/10.1016/j.sintl.2020.100037

Agustí, A., & Hogg, J. C. (2019). Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. *New England Journal of Medicine*, *381*(13), 1248–1256. https://doi.org/10.1056/nejmra1900475

Al-Sheraji, S. H., Ismail, A., Manap, M. Y., Mustafa, S., Yusof, R. M., & Hassan, F. A. (2013). Prebiotics as functional foods: A review. *Journal of Functional Foods*, *5*(4), 1542–1553. https://doi.org/10.1016/j.jff.2013.08.009

Ang, L. Y. E., Too, H. K. I., Tan, E. L., Chow, T.-K. V., Shek, L. P.-C., Tham, E. H., & Alonso, S. (2016). Erratum: Antiviral activity of Lactobacillus reuteri Protectis against Coxsackievirus A and Enterovirus 71 infection in human skeletal muscle and colon cell lines (Virol J. (2016) 13 (111) DOI: 10.1186/s12985-016-0567-6). *Virology Journal*, *13*(1), 1–1. https://doi.org/10.1186/s12985-016-0633-0

Angurana, Suresh K., Bansal, A., Singhi, S., Aggarwal, R., Jayashree, M., Salaria, M., & Mangat, N. K. (2018). Evaluation of effect of probiotics on cytokine levels in critically

Ill children with severe sepsis: A double-blind, placebo-controlled trial. *Critical Care Medicine*, *46*(10), 1656–1664. https://doi.org/10.1097/CCM.0000000000003279

Angurana, Suresh Kumar, & Bansal, A. (2020). Probiotics and COVID-19: Think about the link. *British Journal of Nutrition*. https://doi.org/10.1017/S000711452000361X

Aragón, F., Carino, S., Perdigón, G., & De Moreno De LeBlanc, A. (2015). Inhibition of growth and metastasis of breast cancer in mice by milk fermented with Lactobacillus casei CRL 431. *Journal of Immunotherapy*, *38*(5), 185–196. https://doi.org/10.1097/CJI.0000000000000079

Arthur C Ouwehand, Seppo Salminen, & Erika Isolauri. (2002). Probiotics: an overview of beneficial effects - PubMed. *Antonie van Leeuwenhoek*, *82*(1–4), 279–289.

Barnes, P. J. (2010). Neutrophils find smoke attractive. *Science*, *330*(6000), 40–41. https://doi.org/10.1126/science.1196017

Barnes, P. J. (2018). Targeting cytokines to treat asthma and chronic obstructive pulmonary disease. In *Nature Reviews Immunology*. https://doi.org/10.1038/s41577-018-0006-6

Benjamin Kligler, & Andreas Cohrssen. (2008). Probiotics - PubMed. *American Family Physician*, *1*(8), 1073–1078.

Bermudez-Brito, M., Plaza-Díaz, J., Muñoz-Quezada, S., Gómez-Llorente, C., & Gil, A. (2012). Probiotic Mechanisms of Action. *Annals of Nutrition and Metabolism*, *61*(2), 160–174. https://doi.org/10.1159/000342079

Bhowmik, A., Seemungal, T. A. R., Sapsford, R. J., & Wedzicha, J. A. (2000). Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax*, *55*(2), 114–120. https://doi.org/10.1136/thorax.55.2.114

Blaut, M. (2002). Relationship of prebiotics and food to intestinal microflora. *European Journal of Nutrition*, *41*(SUPPL. 1), 11–16. https://doi.org/10.1007/s00394-002-1102-7

Botić, T., Klingberg, T. D.´., Weingartl, H., & Cencič, A. (2007). A novel eukaryotic cell culture model to study antiviral activity of potential probiotic bacteria. *International Journal of Food Microbiology*, *115*(2), 227–234. https://doi.org/10.1016/j.ijfoodmicro.2006.10.044

Burney, P., Jarvis, D., & Perez-Padilla, R. (2015). The global burden of chronic respiratory disease in adults. *International Journal of Tuberculosis and Lung Disease*, *19*(1), 10–20. https://doi.org/10.5588/ijtld.14.0446

Casas, I. A., & Dobrogosz, W. J. (2000). Validation of the Probiotic Concept: Lactobacillus reuteri confers broad-spectrum protection against disease in humans and animals. *Microbial Ecology in Health and Disease*, *12*(4), 247–285. https://doi.org/10.1080/08910600050216246-1

Cavaglieri, C. R., Nishiyama, A., Fernandes, L. C., Curi, R., Miles, E. A., & Calder, P. C. (2003). Differential effects of short-chain fatty acids on proliferation and production of pro- and anti-inflammatory cytokines by cultured lymphocytes. *Life Sciences*, *73*(13), 1683–1690. https://doi.org/10.1016/S0024-3205(03)00490-9

Celli, B. R., & Barnes, P. J. (2007). Exacerbations of chronic obstructive pulmonary disease. *European Respiratory Journal*, *29*(6), 1224–1238. https://doi.org/10.1183/09031936.00109906

Celli, Bartolomé R., & Wedzicha, J. A. (2019). Update on Clinical Aspects of Chronic Obstructive Pulmonary Disease. *New England Journal of Medicine*, *381*(13), 1257–1266. https://doi.org/10.1056/nejmra1900500

Charalampopoulos, D., & Rastall, R. A. (2012). Prebiotics in foods. *Current Opinion in Biotechnology*, *23*(2), 187–191. https://doi.org/10.1016/j.copbio.2011.12.028

Chhikara, B. S., Rathi, B., & Singh, J. (2020).

Chemical Biology LETTERS Corona virus SARS-CoV-2 disease COVID-19: Infection, prevention and clinical advances of the prospective chemical drug therapeutics. *Chemical Biology Letters Chem. Biol. Lett*, *2020*(1), 63–72.

Chiang, B. L., Sheih, Y. H., Wang, L. H., Liao, C. K., & Gill, H. S. (2000). Enhancing immunity by dietary consumption of a probiotic lactic acid bacterium (Bifidobacterium lactis HN019): Optimization and definition of cellular immune responses. *European Journal of Clinical Nutrition*, *54*(11), 849–855. https://doi.org/10.1038/sj.ejcn.1601093

Choi, H.-J., Song, J.-H., Ahn, Y.-J., Baek, S.-H., & Kwon, D.-H. (2009). Antiviral activities of cell-free supernatants of yogurts metabolites against some RNA viruses. *European Food Research and Technology*, *228*(6), 945–950. https://doi.org/10.1007/s00217-009-1009-0

Chow, J. (2002). Probiotics and prebiotics: A brief overview. *Journal of Renal Nutrition*, *12*(2), 76–86. https://doi.org/10.1053/jren.2002.31759

Coles, L. T., Moughan, P. J., & Darragh, A. J. (2005). In vitro digestion and fermentation methods, including gas production techniques, as applied to nutritive evaluation of foods in the hindgut of humans and other simple-stomached animals. *Animal Feed Science and Technology*, *123-124 Pa*, 421–444. https://doi.org/10.1016/j.anifeedsci.2005.04.021

Cosio, M. G., Saetta, M., & Agusti, A. (2009). Immunologic Aspects of Chronic Obstructive Pulmonary Disease. *New England Journal of Medicine*, *360*(23), 2445–2454. https://doi.org/10.1056/nejmra0804752

Cummings J.H.*, & Macfarlane, G. T. (2002). Gastrointestinal effects of prebiotics. *British Journal of Nutrition*, *87*(6), 145–151. https://doi.org/10.1079/bjnbjn/2002530

Dan W Thomas, & Frank R Greer. (2010). Probiotics and prebiotics in pediatrics . *Pediatrics*, *126*(6), 1217–1231.

de Groot, P. M., Wu, C. C., Carter, B. W., & Munden, R. F. (2018). The epidemiology of lung cancer. *Translational Lung Cancer Research*, *7*(3), 220–233. https://doi.org/10.21037/tlcr.2018.05.06

Dharmage, S. C., Perret, J. L., & Custovic, A. (2019). Epidemiology of asthma in children and adults. *Frontiers in Pediatrics*, *7*(JUN), 246. https://doi.org/10.3389/fped.2019.00246

Dixit, Y., Wagle, A., & Vakil, B. (2016). Patents in the Field of Probiotics, Prebiotics, Synbiotics: A Review. *Journal of Food: Microbiology, Safety & Hygiene*, *01*(02). https://doi.org/10.4172/2476-2059.1000111

Dobler, C. C. (2019). Living well with a chronic respiratory disease. *Breathe*, *15*(2), 93–94. https://doi.org/10.1183/20734735.0196-2019

Douglas, L. C., & Sanders, M. E. (2008). Probiotics and Prebiotics in Dietetics Practice. *Journal of the American Dietetic Association*, *108*(3), 510–521. https://doi.org/10.1016/j.jada.2007.12.009

Emanuel Vamanu, & Adrian Vamanu. (2010). The influence of prebiotics on bacteriocin synthesis using the strain Lactobacillus paracasei CMGB16. *African Journal of Microbiology Research*, *4*(7), 534–537.

Fang, H., Elina, T., Heikki, A., & Seppo, S. (2000). Modulation of humoral immune response through probiotic intake. *FEMS Immunology & Medical Microbiology*, *29*(1), 47–52. https://doi.org/10.1111/j.1574-695x.2000.tb01504.x

Ferkol, T., & Schraufnagel, D. (2014). The global burden of respiratory disease. In *Annals of the American Thoracic Society*. https://doi.org/10.1513/AnnalsATS.201311-405PS

Ferrante, G., & La Grutta, S. (2018). The burden of pediatric asthma. *Frontiers in Pediatrics*, *6*, 186. https://doi.org/10.3389/fped.2018.00186

Fooks, L. J., & Gibson, G. R. (2006). In vitro investigations of the effect of probiotics and prebiotics on selected human intestinal pathogens. *FEMS Microbiology Ecology*, *39*(1), 67–75. https://doi.org/10.1111/j.1574-6941.2002.tb00907.x

Fukushima, Y., Kawata, Y., Hara, H., Terada, A., & Mitsuoka, T. (1998). Effect of a probiotic formula on intestinal immunoglobulin A production in healthy children. *International Journal of Food Microbiology*, *42*(1–2), 39–44. https://doi.org/10.1016/S0168-1605(98)00056-7

Ganesh, B. P., Hall, A., Ayyaswamy, S., Nelson, J. W., Fultz, R., Major, A., Haag, A., Esparza, M., Lugo, M., Venable, S., Whary, M., Fox, J. G., & Versalovic, J. (2018). Diacylglycerol kinase synthesized by commensal Lactobacillus reuteri diminishes protein kinase C phosphorylation and histamine-mediated signaling in the mammalian intestinal epithelium. *Mucosal Immunology*, *11*(2), 380–393. https://doi.org/10.1038/mi.2017.58

Gao, C., Ganesh, B. P., Shi, Z., Shah, R. R., Fultz, R., Major, A., Venable, S., Lugo, M., Hoch, K., Chen, X., Haag, A., Wang, T. C., & Versalovic, J. (2017). Gut Microbe–Mediated Suppression of Inflammation-Associated Colon Carcinogenesis by Luminal Histamine Production. *American Journal of Pathology*, *187*(10), 2323–2336. https://doi.org/10.1016/j.ajpath.2017.06.011

Ghadimi, D., Fölster-Holst, R., de Vrese, M., Winkler, P., Heller, K. J., & Schrezenmeir, J. (2008). Effects of probiotic bacteria and their genomic DNA on TH1/TH2-cytokine production by peripheral blood mononuclear cells (PBMCs) of healthy and allergic subjects. *Immunobiology*, *213*(8), 677–692. https://doi.org/10.1016/j.imbio.2008.02.001

Gibson, G. R., Probert, H. M., Loo, J. Van, Rastall, R. A., & Roberfroid, M. B. (2004). Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. *Nutrition Research Reviews*, *17*(2), 259–275. https://doi.org/10.1079/nrr200479

Gill, H., & Prasad, J. (2008). Probiotics, immunomodulation, and health benefits. In *Advances in Experimental Medicine and Biology* (Vol. 606, pp. 423–454). Springer New York. https://doi.org/10.1007/978-0-387-74087-4_17

Gill, H. S., Rutherfurd, K. J., & Cross, M. L. (2001). Dietary probiotic supplementation enhances natural killer cell activity in the elderly: An investigation of age-related immunological changes. *Journal of Clinical Immunology*, *21*(4), 264–271. https://doi.org/10.1023/A:1010979225018

Gill, Harsharnjit S. (2003). Probiotics to enhance anti-infective defences in the gastrointestinal tract. *Bailliere's Best Practice and Research in Clinical Gastroenterology*, *17*(5), 755–773. https://doi.org/10.1016/S1521-6918(03)00074-X

Giovannini, M., Agostoni, C., Riva, E., Salvini, F., Ruscitto, A., Zuccotti, G. V., Radaelli, G., Besana, R., Biasucci, G., Galluzzo, C., Longhi, R., Podestà, A., & Sterpa, A. (2007). A randomized prospective double blind controlled trial on effects of long-term consumption of fermented milk containing Lactobacillus casei in pre-school children with allergic asthma and/or rhinitis. *Pediatric Research*, *62*(2), 215–220. https://doi.org/10.1203/PDR.0b013e3180a76d94

Gui, Q. F., Lu, H. F., Zhang, C. X., Xu, Z. R., & Yang, Y. M. (2015). Well-balanced commensal microbiota contributes to anti-cancer response in a lung cancer mouse model. *Genetics and Molecular Research*, *14*(2), 5642–5651. https://doi.org/10.4238/2015.May.25.16

Gupta, V., & Garg, R. (2009). Probiotics. *Indian Journal of Medical Microbiology*, *27*(3), 202. https://doi.org/10.4103/0255-0857.53201

Halpern, G. M., Vruwink, K. G., Water, J. A. Van de, Keen, C. L., & Gershwin, M. E. (1991). Influence of long-term yoghurt consumption in young adults. *International*

Journal of Immunotherapy, *7*(4), 205–210.

Hamid, Q., & Tulic, M. (2009). Immunobiology of asthma. *Annual Review of Physiology*, *71*, 489–507.

Han, K. J., Lee, N. K., Park, H., & Paik, H. D. (2015). Anticancer and anti-inflammatory activity of probiotic lactococcus lactis nk34. *Journal of Microbiology and Biotechnology*, *25*(10), 1697–1701. https://doi.org/10.4014/jmb.1503.03033

Hao, Q., Dong, B. R., & Wu, T. (2015). Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database of Systematic Reviews*, *2015*(2). https://doi.org/10.1002/14651858.CD006895.pub3

Harata, G., He, F., Kawase, M., Hosono, A., Takahashi, K., & Kaminogawa, S. (2009). Differentiated implication of Lactobacillus GG and L. gasseri TMC0356 to immune responses of murine Peyer's patch. *Microbiology and Immunology*, *53*(8), 475–480. https://doi.org/10.1111/j.1348-0421.2009.00146.x

Helwig, U., Lammers, K. M., Rizzello, F., Brigidi, P., Rohleder, V., Caramelli, E., Gionchetti, P., Schrezenmeir, J., Foelsch, U. R., Schreiber, S., & Campieri, M. (2006). Lactobacilli, bifidobacteria and E. coli nissle induce pro- and anti-inflammatory cytokines in peripheral blood mononuclear cells. *World Journal of Gastroenterology*, *12*(37), 5978–5986. https://doi.org/10.3748/wjg.v12.i37.5978

Hirsch, F. R., Scagliotti, G. V., Mulshine, J. L., Kwon, R., Curran, W. J., Wu, Y. L., & Paz-Ares, L. (2017). Lung cancer: current therapies and new targeted treatments. *The Lancet*, *389*(10066), 299–311. https://doi.org/10.1016/S0140-6736(16)30958-8

Hogg, J. C., Chu, F., Utokaparch, S., Woods, R., Elliott, W. M., Buzatu, L., Cherniack, R. M., Rogers, R. M., Sciurba, F. C., Coxson, H. O., & Paré, P. D. (2004). The Nature of Small-Airway Obstruction in Chronic Obstructive Pulmonary Disease. *New England Journal of Medicine*, *350*(26), 2645–2653. https://doi.org/10.1056/nejmoa032158

Holtzman, M. J., Byers, D. E., Benoit, L. A., Battaile, J. T., You, Y., Agapov, E., Park, C., Grayson, M. H., Kim, E. Y., & Patel, A. C. (2009). Chapter 5 Immune Pathways for Translating Viral Infection into Chronic Airway Disease1. *Advances in Immunology*, *102*, 245–276. https://doi.org/10.1016/S0065-2776(09)01205-X

Hosono, A., Kashina, T., & Kada, T. (1986). Antimutagenic Properties of Lactic Acid-Cultured Milk on Chemical and Fecal Mutagens. *Journal of Dairy Science*, *69*(9), 2237–2242. https://doi.org/10.3168/jds.S0022-0302(86)80662-2

Hussain, M. S., Mohit, Pamma, P., & Kumari, B. (2021). Treatment Modalities of the Covid-19 Pandemic Through Repurposed Drugs and Status of Vaccines. *International Journal of Applied Pharmaceutics*, *13*(2), 48–58.

Iida, N., Dzutsev, A., Stewart, C. A., Smith, L., Bouladoux, N., Weingarten, R. A., Molina, D. A., Salcedo, R., Back, T., Cramer, S., Dai, R. M., Kiu, H., Cardone, M., Naik, S., Patri, A. K., Wang, E., Marincola, F. M., Frank, K. M., Belkaid, Y., … Goldszmid, R. S. (2013). Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science*, *342*(6161), 967–970. https://doi.org/10.1126/science.1240527

Infusino, F., Marazzato, M., Mancone, M., Fedele, F., Mastroianni, C. M., Severino, P., Ceccarelli, G., Santinelli, L., Cavarretta, E., Marullo, A. G. M., Miraldi, F., Carnevale, R., Nocella, C., Biondi-Zoccai, G., Pagnini, C., Schiavon, S., Pugliese, F., Frati, G., & D'Ettorre, G. (2020). Diet supplementation, probiotics, and nutraceuticals in SARS-CoV-2 infection: A scoping review. *Nutrients*, *12*(6), 1–21. https://doi.org/10.3390/nu12061718

Isolauri, E., Joensuu, J., Suomalainen, H., Luomala, M., & Vesikari, T. (1995).

Improved immunogenicity of oral D x RRV reassortant rotavirus vaccine by Lactobacillus casei GG. *Vaccine*, *13*(3), 310–312. https://doi.org/10.1016/0264-410X(95)93319-5

Isolauri, E., Salminen, S., & Ouwehand, A. C. (2004). Probiotics. *Best Practice and Research: Clinical Gastroenterology*, *18*(2), 299–313. https://doi.org/10.1016/j.bpg.2003.10.006

Izumo, T., Maekawa, T., Ida, M., Noguchi, A., Kitagawa, Y., Shibata, H., Yasui, H., & Kiso, Y. (2010). Effect of intranasal administration of Lactobacillus pentosus S-PT84 on influenza virus infection in mice. *International Immunopharmacology*, *10*(9), 1101–1106. https://doi.org/10.1016/j.intimp.2010.06.012

Jajodia, A., Ebner, L., Heidinger, B., Chaturvedi, A., & Prosch, H. (2020). Imaging in corona virus disease 2019 (COVID-19)—A Scoping review. *European Journal of Radiology Open*, *7*. https://doi.org/10.1016/j.ejro.2020.100237

Jang, S. O., Kim, H. J., Kim, Y. J., Kang, M. J., Kwon, J. W., Seo, J. H., Kim, H. Y., Kim, B. J., Yu, J., & Hong, S. J. (2012). Asthma prevention by Lactobacillus rhamnosus in a mouse model is associated with CD4 +CD25 +Foxp3 +T cells. *Allergy, Asthma and Immunology Research*, *4*(3), 150–156. https://doi.org/10.4168/aair.2012.4.3.150

Kaila, M., Isolauri, E., Soppi, E., Virtanen, E., Laine, S., & Arvilommi, H. (1992). Enhancement of the circulating antibody secreting cell response in human diarrhea by a human Lactobacillus strain. *Pediatric Research*, *32*(2), 141–144. https://doi.org/10.1203/00006450-199208000-00002

Kang, M. J., Chun, G. L., Lee, J. Y., Dela Cruz, C. S., Chen, Z. J., Enelow, R., & Elias, J. A. (2008). Cigarette smoke selectively enhances viral PAMP- and virus-induced pulmonary innate immune and remodeling responses in mice. *Journal of Clinical Investigation*, *118*(8), 2771–2784. https://doi.org/10.1172/JCI32709

Kaur, I. P., Chopra, K., & Saini, A. (2002). Probiotics: Potential pharmaceutical applications. *European Journal of Pharmaceutical Sciences*, *15*(1), 1–9. https://doi.org/10.1016/S0928-0987(01)00209-3

Kawai, T., & Akira, S. (2006). Innate immune recognition of viral infection. *Nature Immunology*, *7*(2), 131–137. https://doi.org/10.1038/ni1303

Kishi, A., Uno, K., Matsubara, Y., Okuda, C., & Kishida, T. (1996). Effect of the oral administration of Lactobacillus brevis subsp. coagulans on interferon-alpha producing capacity in humans. *Journal of the American College of Nutrition*, *15*(4), 408–412. https://doi.org/10.1080/07315724.1996.10718617

Kolida, S., & Gibson, G. R. (2011). Synbiotics in health and disease. *Annual Review of Food Science and Technology*, *2*, 373–393. https://doi.org/10.1146/annurev-food-022510-133739

Kumar, M., Kumar, A., Nagpal, R., Mohania, D., Behare, P., Verma, V., Kumar, P., Poddar, D., Aggarwal, P. K., Henry, C. J. K., Jain, S., & Yadav, H. (2010). Cancer-preventing attributes of probiotics: An update. *International Journal of Food Sciences and Nutrition*, *61*(5), 473–496. https://doi.org/10.3109/09637480903455971

Kumar, P., & Ram, U. (2017). Patterns, factors associated and morbidity burden of asthma in India. *PLOS ONE*, *12*(10), e0185938. https://doi.org/10.1371/journal.pone.0185938

KUMARI, R., KAUR, J., & HUSSAIN, S. (2020). MANAGEMENT OF DIABETES WITH COVID-19: A REVIEW. *International Journal of Pharmacy and Pharmaceutical Sciences*, 1–6. https://doi.org/10.22159/ijpps.2020v12i12.39968

Lambrecht, B. N., & Hammad, H. (2015). The immunology of asthma. *Nature*

Immunology, *16*(1), 45–56. https://doi.org/10.1038/ni.3049

Lambrecht, B. N., Hammad, H., & Fahy, J. V. (2019). The Cytokines of Asthma. In *Immunity*. https://doi.org/10.1016/j.immuni.2019.03.018

Lee, N.-K., Han, K. J., Son, S.-H., Eom, S. J., Lee, S.-K., & Paik, H.-D. (2015). Multifunctional effect of probiotic Lactococcus lactis KC24 isolated from kimchi. *LWT - Food Science and Technology*, *64*(2), 1036–1041. https://doi.org/10.1016/j.lwt.2015.07.019

Lehtoranta, L., Pitkäranta, A., & Korpela, R. (2014). Probiotics in respiratory virus infections. *European Journal of Clinical Microbiology and Infectious Diseases*, *33*(8), 1289–1302. https://doi.org/10.1007/s10096-014-2086-y

Licht, T. R., Ebersbach, T., & Frøkiær, H. (2012). Prebiotics for prevention of gut infections. *Trends in Food Science and Technology*, *23*(2), 70–82. https://doi.org/10.1016/j.tifs.2011.08.011

Link-Amster, H., Rochat, F., Saudan, K. Y., Mignot, O., & Aeschlimann, J. M. (1994). Modulation of a specific humoral immune response and changes in intestinal flora mediated through fermented milk intake. *FEMS Immunology and Medical Microbiology*, *10*(1), 55–63. https://doi.org/10.1111/j.1574-695X.1994.tb00011.x

Liu, P. C., Yan, Y. K., Ma, Y. J., Wang, X. W., Geng, J., Wang, M. C., Wei, F. X., Zhang, Y. W., Xu, X. D., & Zhang, Y. C. (2017). Probiotics reduce postoperative infections in patients undergoing colorectal surgery: A systematic review and meta-analysis. *Gastroenterology Research and Practice*, *2017*. https://doi.org/10.1155/2017/6029075

Liu, Y., Fatheree, N. Y., Mangalat, N., & Rhoads, J. M. (2012). Lactobacillus reuteri strains reduce incidence and severity of experimental necrotizing enterocolitis via modulation of TLR4 and NF-κB signaling in the intestine. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *302*(6). https://doi.org/10.1152/ajpgi.00266.2011

Liu, Y., Tran, D. Q., & Rhoads, J. M. (2018). Probiotics in Disease Prevention and Treatment. *Journal of Clinical Pharmacology*, *58*(December 2017), S164–S179. https://doi.org/10.1002/jcph.1121

Lucas, M., Schachterle, W., Oberle, K., Aichele, P., & Diefenbach, A. (2007). Dendritic Cells Prime Natural Killer Cells by trans-Presenting Interleukin 15. *Immunity*, *26*(4), 503–517. https://doi.org/10.1016/j.immuni.2007.03.006

Macfarlane, S., Macfarlane, G. T., & Cummings, J. H. (2006). Review article: Prebiotics in the gastrointestinal tract. *Alimentary Pharmacology and Therapeutics*, *24*(5), 701–714. https://doi.org/10.1111/j.1365-2036.2006.03042.x

Majamaa, H., Isolauri, E., Saxelin, M., & Vesikari, T. (1995). Lactic acid bacteria in the treatment of acute rotavirus gastroenteritis. *Journal of Pediatric Gastroenterology and Nutrition*, *20*(3), 333–383. https://doi.org/10.1097/00005176-199504000-00012

Makino, S., Ikegami, S., Kume, A., Horiuchi, H., Sasaki, H., & Orii, N. (2010). Reducing the risk of infection in the elderly by dietary intake of yoghurt fermented with Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1. *British Journal of Nutrition*, *104*(7), 998–1006. https://doi.org/10.1017/S000711451000173X

Malik, Y. S., Kumar, N., Sircar, S., Kaushik, R., Bhat, S., Dhama, K., Gupta, P., Goyal, K., Singh, M. P., Ghoshal, U., El Zowalaty, M. E., Vinodhkumar, O. R., Yatoo, M. I., Tiwari, R., Pathak, M., Patel, S. K., Sah, R., Rodriguez-Morales, A. J., Ganesh, B., … Singh, R. K. (2020). Coronavirus disease pandemic (Covid-19): Challenges and a global perspective. *Pathogens*, *9*(7), 1–31.

https://doi.org/10.3390/pathogens9070519

Mandal, V., Sen, S. K., & Mandal, N. C. (2009). Effect of prebiotics on bacteriocin production and cholesterol lowering activity of Pediococcus acidilactici LAB 5. *World Journal of Microbiology and Biotechnology*, *25*(10), 1837–1847. https://doi.org/10.1007/s11274-009-0085-4

Markowiak, P., & Ślizewska, K. (2017). Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients*, *9*(9), 1021. https://doi.org/10.3390/nu9091021

Merenstein, D., Murphy, M., Fokar, A., Hernandez, R. K., Park, H., Nsouli, H., Sanders, M. E., Davis, B. A., Niborski, V., Tondu, F., & Shara, N. M. (2010). Use of a fermented dairy probiotic drink containing Lactobacillus casei (DN-114 001) to decrease the rate of illness in kids: The DRINK study A patient-oriented, double-blind, cluster-randomized, placebo-controlled, clinical trial. *European Journal of Clinical Nutrition*, *64*(7), 669–677. https://doi.org/10.1038/ejcn.2010.65

Mian, M. F., Lauzon, N. M., Stämpfli, M. R., Mossman, K. L., & Ashkar, A. A. (2008). Impairment of human NK cell cytotoxic activity and cytokine release by cigarette smoke. *Journal of Leukocyte Biology*, *83*(3), 774–784. https://doi.org/10.1189/jlb.0707481

Miettinen, M., Vuopio-Varkila, J., & Varkila, K. (1996). Production of human tumor necrosis factor alpha, interleukin-6, and interleukin-10 is induced by lactic acid bacteria. *Infection and Immunity*, *64*(12), 5403–5405. https://doi.org/10.1128/iai.64.12.5403-5405.1996

Mishra, S. S., Behera, P. K., Kar, B., & Ray, R. C. (2018). Advances in Probiotics, Prebiotics and Nutraceuticals. In Swati Sakambari Mishra, Prafulla Kumar Behera, Biswabandita Kar, & Ramesh C. Ray (Eds.), *Innovations in Technologies for Fermented Food and Beverage Industries* (pp. 121–141). Springer International Publishing. https://doi.org/10.1007/978-3-319-74820-7_7

Mohanty, D., Misra, S., Mohapatra, S., & Sahu, P. S. (2018). Prebiotics and synbiotics: Recent concepts in nutrition. *Food Bioscience*, *26*, 152–160. https://doi.org/10.1016/j.fbio.2018.10.008

Mohit, & Hussain, M. S. (2021). Potential Role of Curcumin As a Treatment Option For COVID-19: A Review. *Plant Archives*, *21*(1).

Morimoto, K., Takeshita, T., Nanno, M., Tokudome, S., & Nakayama, K. (2005). Modulation of natural killer cell activity by supplementation of fermented milk containing Lactobacillus casei in habitual smokers. *Preventive Medicine*, *40*(5), 589–594. https://doi.org/10.1016/j.ypmed.2004.07.019

Mortaz, E., Adcock, I. M., Folkerts, G., Barnes, P. J., Paul Vos, A., & Garssen, J. (2013). Probiotics in the management of lung diseases. *Mediators of Inflammation*, *2013*. https://doi.org/10.1155/2013/751068

Naruszewicz, M., Johansson, M.-L., Zapolska-Downar, D., & Bukowska, H. (2002). Effect of Lactobacillus plantarum 299v on cardiovascular disease risk factors in smokers. *The American Journal of Clinical Nutrition*, *76*(6), 1249–1255. https://doi.org/10.1093/ajcn/76.6.1249

Newman, K. C., & Riley, E. M. (2007). Whatever turns you on: Accessory-cell-dependent activation of NK cells by pathogens. *Nature Reviews Immunology*, *7*(4), 279–291. https://doi.org/10.1038/nri2057

Noverr, M. C., & Huffnagle, G. B. (2005). The "microflora hypothesis" of allergic diseases. *Clinical and Experimental Allergy*, *35*(12), 1511–1520. https://doi.org/10.1111/j.1365-2222.2005.02379.x

Nurmi, J. T., Puolakkainen, P. A., & Rautonen, N. E. (2005). Bifidobacterium lactis sp. 420 up-regulates cyclooxygenase (Cox)-1 and down-regulates Cox-2 gene expression in a caco-2 cell culture model. *Nutrition and Cancer*, *51*(1), 83–92. https://doi.org/10.1207/s15327914nc5101_

12

Olaimat, A. N., Aolymat, I., Al-Holy, M., Ayyash, M., Abu Ghoush, M., Al-Nabulsi, A. A., Osaili, T., Apostolopoulos, V., Liu, S. Q., & Shah, N. P. (2020). The potential application of probiotics and prebiotics for the prevention and treatment of COVID-19. *Npj Science of Food*, *4*(1), 1–7. https://doi.org/10.1038/s41538-020-00078-9

Olivares, M., Díaz-Ropero, M. P., Gómez, N., Sierra, S., Lara-Villoslada, F., Martín, R., Rodríguez, J. M., & Xaus, J. (2006). Dietary deprivation of fermented foods causes a fall in innate immune response. Lactic acid bacteria can counteract the immunological effect of this deprivation. *Journal of Dairy Research*, *73*(4), 492–498. https://doi.org/10.1017/S0022029906002068

Orange, J. S., Wang, B., Terhorst, C., & Biron, C. A. (1995). Requirement for natural killer cell-produced interferon γ in defense against murine cytomegalovirus infection and enhancement of this defense pathway by interleukin 12 administration. *Journal of Experimental Medicine*, *182*(4), 1045–1056. https://doi.org/10.1084/jem.182.4.1045

Ortaldo, J. R., Winkler-Pickett, R. T., Yagita, H., & Young, H. A. (1991). Comparative studies of CD3- and CD3+ CD56+ cells: Examination of morphology, functions, T cell receptor rearrangement, and pore-forming protein expression. *Cellular Immunology*, *136*(2), 486–495. https://doi.org/10.1016/0008-8749(91)90369-M

Pandey, K. R., Naik, S. R., & Vakil, B. V. (2015). Probiotics, prebiotics and synbiotics- a review. *Journal of Food Science and Technology*, *52*(12), 7577–7587. https://doi.org/10.1007/s13197-015-1921-1

Patel, R. M., & Denning, P. W. (2013). Therapeutic Use of Prebiotics, Probiotics, and Postbiotics to Prevent Necrotizing Enterocolitis. What is the Current Evidence? *Clinics in Perinatology*, *40*(1), 11–25. https://doi.org/10.1016/j.clp.2012.12.002

Patel, S., & Goyal, A. (2012). The current trends and future perspectives of prebiotics research: a review. *3 Biotech*, *2*(2), 115–125. https://doi.org/10.1007/s13205-012-0044-x

Peng, M., & Biswas, D. (2017). Short chain and polyunsaturated fatty acids in host gut health and foodborne bacterial pathogen inhibition. *Critical Reviews in Food Science and Nutrition*, *57*(18), 3987–4002. https://doi.org/10.1080/10408398.2016.1203286

Pool-Zobel, B. L. (2005). Inulin-type fructans and reduction in colon cancer risk: review of experimental and human data. *British Journal of Nutrition*, *93*(S1), S73–S90. https://doi.org/10.1079/bjn20041349

Pool-Zobel, B. L., & Sauer, J. (2007). Overview of experimental data on reduction of colorectal cancer risk by inulin-type fructans. *Journal of Nutrition*, *137*(11), 2580–2584. https://doi.org/10.1093/jn/137.11.2580s

Raman, M., Ambalam, P., Kondepudi, K. K., Pithva, S., Kothari, C., Patel, A. T., Purama, R. K., Dave, J. M., & Vyas, B. R. M. (2013). Potential of probiotics, prebiotics and synbiotics for management of colorectal cancer. *Gut Microbes*, *4*(3), 181–192. https://doi.org/10.4161/gmic.23919

Rastall, R. A., & Maitin, V. (2002). Prebiotics and synbiotics: Towards the next generation. *Current Opinion in Biotechnology*, *13*(5), 490–496. https://doi.org/10.1016/S0958-1669(02)00365-8

Rennard, S. I., & Vestbo, J. (2006). COPD: the dangerous underestimate of 15%. *Lancet*, *367*(9518), 1216–1219. https://doi.org/10.1016/S0140-6736(06)68516-4

Ringø, E., Olsen, R. E., Gifstad, T., Dalmo, R. A., Amlund, H., Hemre, G. I., & Bakke, A. M. (2010). Prebiotics in aquaculture: A review. *Aquaculture Nutrition*, *16*(2), 117–136. https://doi.org/10.1111/j.1365-2095.2009.00731.x

Roberfroid, M. (2007). Prebiotics: The concept revisited. *Journal of Nutrition*, *137*(3).

https://doi.org/10.1093/jn/137.3.830s

S, T., & Hussain MS. (2021). Functional Foods for prevention and treatment of cancer. *Asian Journal of Pharmaceutical and Clinical Research*, *14*(3), 4–10.

Salminen, S., Ouwehand, A., Benno, Y., & Lee, Y. K. (1999). Probiotics: How should they be defined? *Trends in Food Science and Technology*, *10*(3), 107–110. https://doi.org/10.1016/S0924-2244(99)00027-8

Salvi, S., Kumar, G. A., Dhaliwal, R. S., Paulson, K., Agrawal, A., Koul, P. A., Mahesh, P. A., Nair, S., Singh, V., Aggarwal, A. N., Christopher, D. J., Guleria, R., Mohan, B. V. M., Tripathi, S. K., Ghoshal, A. G., Kumar, R. V., Mehrotra, R., Shukla, D. K., Dutta, E., … Dandona, L. (2018). The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990–2016. *The Lancet Global Health*, *6*(12), e1363–e1374. https://doi.org/10.1016/S2214-109X(18)30409-1

Sapey, E., & Stockley, R. A. (2006). COPD exacerbations·2: Aetiology. *Thorax*, *61*(3), 250–258. https://doi.org/10.1136/thx.2005.041822

Scharton, T. M., & Scott, P. (1993). Natural killer cells are a source of interferon γ that drives differentiation of CD4+ T cell subsets and induces early resistance to leishmania major in mice. *Journal of Experimental Medicine*, *178*(2), 567–578. https://doi.org/10.1084/jem.178.2.567

Schrezenmeir, J., & De Vrese, M. (2001). Probiotics, prebiotics, and synbiotics - Approaching a definition. *American Journal of Clinical Nutrition*, *73*(2 SUPPL.). https://doi.org/10.1093/ajcn/73.2.361s

Schroder, K., Hertzog, P. J., Ravasi, T., & Hume, D. A. (2004). Interferon-γ: an overview of signals, mechanisms and functions. *Journal of Leukocyte Biology*, *75*(2), 163–189. https://doi.org/10.1189/jlb.0603252

Serkova, M. I., Urtenova, M. A., Tkachenko, E. I., Avalueva, E. B., Orlov, S. V., Ivanov, S. V., Orishak, E. A., & Skazyvaeva, E. V. (2013). [On the possibilities of correction of changes of the gastrointestinal tract microbiota in patients with lung cancer treated receiving chemotherapy]. *Ėksperimental'nai{combining Double Inverted Breve}a i Klinicheskai{combining Double Inverted Breve}a Gastroėnterologii{combining Double Inverted Breve}a = Experimental & Clinical Gastroenterology*, *11*, 15–20.

Sheih, Y. H., Chiang, B. L., Wang, L. H., Liao, C. K., & Gill, H. S. (2001). Systemic immunity-enhancing effects in healthy subjects following dietary consumption of the lactic acid bacterium Lactobacillus rhamnosus HN001. *Journal of the American College of Nutrition*, *20*(2), 149–156. https://doi.org/10.1080/07315724.2001.10719027

Shida, K., Sato, T., Iizuka, R., Hoshi, R., Watanabe, O., Igarashi, T., Miyazaki, K., Nanno, M., & Ishikawa, F. (2017). Daily intake of fermented milk with Lactobacillus casei strain Shirota reduces the incidence and duration of upper respiratory tract infections in healthy middle-aged office workers. *European Journal of Nutrition*, *56*(1), 45–53. https://doi.org/10.1007/s00394-015-1056-1

Siegel, R. L., Miller, K. D., & Jemal, A. (2018). Cancer statistics, 2018. *CA: A Cancer Journal for Clinicians*, *68*(1), 7–30. https://doi.org/10.3322/caac.21442

Slavin, J. (2013). Fiber and prebiotics: Mechanisms and health benefits. *Nutrients*, *5*(4), 1417–1435. https://doi.org/10.3390/nu5041417

Soccol, C. R., Vandenberghe, L. P. de S., Spier, M. R., Medeiros, A. B. P., Yamaguishi, C. T., Lindner, J. D. D., Pandey, A., & Thomaz-Soccol, V. (2010). The potential of probiotics: a review. *Food Technology and Biotechnology*, *48*(4), 413–434.

Solis Pereyra, B., & Lemonnier, D. (1993). Induction of human cytokines by bacteria used in dairy foods. *Nutrition Research*, *13*(10), 1127–1140. https://doi.org/10.1016/S0271-5317(05)80737-7

Soriano, J. B., Kendrick, P. J., Paulson, K. R., Gupta, V., Abrams, E. M., Adedoyin, R. A., Adhikari, T. B., Advani, S. M., Agrawal, A., Ahmadian, E., Alahdab, F., Aljunid, S. M., Altirkawi, K. A., Alvis-Guzman, N., Anber, N. H., Andrei, C. L., Anjomshoa, M., Ansari, F., Antó, J. M., … Vos, T. (2020). Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Respiratory Medicine*, *8*(6), 585–596. https://doi.org/10.1016/S2213-2600(20)30105-3

Strowig, T., Brilot, F., & Münz, C. (2008). Noncytotoxic Functions of NK Cells: Direct Pathogen Restriction and Assistance to Adaptive Immunity. *The Journal of Immunology*, *180*(12), 7785–7791. https://doi.org/10.4049/jimmunol.180.12.7785

Su, S., Wong, G., Shi, W., Liu, J., Lai, A. C. K., Zhou, J., Liu, W., Bi, Y., & Gao, G. F. (2016). Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. *Trends in Microbiology*, *24*(6), 490–502. https://doi.org/10.1016/j.tim.2016.03.003

Taipale, T., Pienihkkinen, K., Isolauri, E., Larsen, C., Brockmann, E., Alanen, P., Jokela, J., & Söderling, E. (2011). Bifidobacterium animalis subsp. lactis BB-12 in reducing the risk of infections in infancy. *British Journal of Nutrition*, *105*(3), 409–416. https://doi.org/10.1017/S0007114510003685

Tanasienko, O. A., Cheremshenko, N. L., Titova, G. P., Potebnya, M. G., Gavrilenko, M. M., Nagorna, S. S., & Kovalenko, N. K. (2005). Elevation of the efficacy of antitumor vaccine prepared on the base of lectines from B. subtilis B-7025 upon its combined application with probiotics in vivo. *Exp Oncol*, *27*(4), 336–338.

Taylor, A. L., Dunstan, J. A., & Prescott, S. L. (2007). Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: A randomized controlled trial. *Journal of Allergy and Clinical Immunology*, *119*(1), 184–191. https://doi.org/10.1016/j.jaci.2006.08.036

Thomas, C. M., & Versalovic, J. (2010). Probiotics-host communication modulation of signaling pathways in the intestine. *Gut Microbes*, *1*(3), 1–16. https://doi.org/10.4161/gmic.1.3.11712

Van Der Aa, L. B., Van Aalderen, W. M. C., Heymans, H. S. A., Henk Sillevis Smitt, J., Nauta, A. J., Knippels, L. M. J., Ben Amor, K., & Sprikkelman, A. B. (2011). Synbiotics prevent asthma-like symptoms in infants with atopic dermatitis. *Allergy: European Journal of Allergy and Clinical Immunology*, *66*(2), 170–177. https://doi.org/10.1111/j.1398-9995.2010.02416.x

Wang, D. Y., Ghoshal, A. G., Bin Abdul Muttalif, A. R., Lin, H. C., Thanaviratananich, S., Bagga, S., Faruqi, R., Sajjan, S., Brnabic, A. J. M., Dehle, F. C., & Cho, S. H. (2016). Quality of Life and Economic Burden of Respiratory Disease in Asia-Pacific-Asia-Pacific Burden of Respiratory Diseases Study. *Value in Health Regional Issues*. https://doi.org/10.1016/j.vhri.2015.11.004

Wheeler, J. G., Shema, S. J., Bogle, M. L., Shirrell, M. A., Burks, A. W., Pittler, A., & Helm, R. M. (1997). Immune and clinical impact of Lactobacillus acidophilus on asthma. *Annals of Allergy, Asthma and Immunology*, *79*(3), 229–233. https://doi.org/10.1016/S1081-1206(10)63007-4

Williams, N. T. (2010). Probiotics. *American Journal of Health-System Pharmacy*, *67*(6), 449–458. https://doi.org/10.2146/ajhp090168

Xu, K., Cai, H., Shen, Y., Ni, Q., Chen, Y., Hu, S., Li, J., Wang, H., Yu, L., Huang, H., Qiu, Y., Wei, G., Fang, Q., Zhou, J., Sheng, J., Liang, T., & Li, L. (2020). Management of COVID-19: the Zhejiang experience. *Zhejiang Da Xue Xue Bao. Yi Xue Ban = Journal of Zhejiang University. Medical Sciences*, *49*(2), 147–157. https://doi.org/10.3785/j.issn.1008-9292.2020.02.02

Yoo, J., Tcheurekdjian, H., Lynch, S. V., Cabana, M., & Boushey, H. A. (2007). Microbial manipulation of immune function for asthma prevention inferences from clinical trials. *Proceedings of the American Thoracic Society*, *4*(3), 277–282. https://doi.org/10.1513/pats.200702-033AW

Zamberi, N. R., Abu, N., Mohamed, N. E., Nordin, N., Keong, Y. S., Beh, B. K., Zakaria, Z. A. B., Nik Abdul Rahman, N. M. A., & Alitheen, N. B. (2016). The Antimetastatic and Antiangiogenesis Effects of Kefir Water on Murine Breast Cancer Cells. *Integrative Cancer Therapies*, *15*(4), NP53–NP66. https://doi.org/10.1177/1534735416642862

Zelaya, H., Alvarez, S., Kitazawa, H., & Villena, J. (2016). Respiratory antiviral immunity and immunobiotics: Beneficial effects on inflammation-coagulation interaction during influenza virus infection. *Frontiers in Immunology*, *7*(DEC), 1. https://doi.org/10.3389/fimmu.2016.00633

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