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Review

Antiviral activity of fermented foods and their probiotics bacteria towards respiratory and alimentary tracts viruses

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ABSTRACT

The recent COVID-19, a viral outbreak calls for a high demand for non-conventional antiviral agents that can reduce the risk of infections and promote fast recovery. Fermented foods and their probiotics bacteria have recently received increasing interest due to the reported potential of high antiviral activity. Several probiotics strains demonstrated broad range of antiviral activities and different mechanisms of action. This article will review the diversity, health benefits, interaction with immune system and antiviral activity of fermented foods and their probiotics bacteria. In addition, the mechanisms of action will be reviewed to determine the broad range potential antiviral activity against the respiratory and alimentary tracts viruses. The probiotics bacteria and bioactive compounds in fermented foods demonstrated antiviral activities against respiratory and alimentary tracts viruses. The mechanism of action was reported to be due to the stimulation of the immune system function via enhancing natural killers cell toxicity, enhance the production of pro-inflammatory cytokines, and increasing the cytotoxic of T lymphocytes (CD3⁺, CD16⁺, CD56⁺). However, further studies are highly recommended to determine the potential antiviral activity for traditional fermented foods.

1. Introduction

Fermented foods are found as heritage foods in every part of the world. Their diversity highly depends on communities' dietary habits and the availability of the raw materials. Asian and South Asian regions have abundant and diverse fermented foods produced from both plant-based raw commodities such as soybeans to produce tempeh (Sanjukta & Rai, 2016), cabbage to produce *kimchi* (Lee, Whon, Roh, & Jeon, 2020), durian to produce *tempoyak* (Khalil et al., 2018) and glutinous rice *tapai* (Raji, Ab Karim, Ishak, & Arshad, 2017). In addition, fermented fish, shrimp paste, and fish sauce are known fermented foods in most of the Asian countries (Saisithi, 1994). Fermented dairy products and sourdough bread are the main fermented foods in European countries, Middle East and North Africa (Nair & Prajapati, 2003). Cheese and alcoholic beverages are the most common fermented foods in North America, while sorghum and maize are used for the production of

fermented porridges in South America (Tamang et al., 2020). Traditional fermented foods are produced via spontaneous fermentation process as those found in Asia, Middle East and Africa. Traditional fermentation process is very valuable because of the unique taste and aroma of the end products, and the microbial diversity of the fermentation (Tamang, Watanabe, & Holzapfel, 2016). However, controlled fermentation using selective starter cultures in the commercialized fermentation processes can consistently generate broad range of biological entities such as antioxidant and antimicrobial agent due to the production of new metabolites which is not present or present at low concentrations in the raw materials (Muhialdin, Kadum, Zarei, & Husin, 2020). Moreover, the defined starter cultures can inhibit the growth of pathogens during the fermentation and enhance the safety of the fermented foods (Marsilio et al., 2005). Lactic acid bacteria (LAB) are the major fermentation microorganisms that contribute to the chemical changes and flavour development for the spontaneous and controlled

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fermentations (de Souza & Dias, 2017).

LAB is a major group of commensal bacteria and certain strains are well known for their probiotic's properties especially Lactobacilli that are commonly found in all fermented foods (Marco et al., 2017). Probiotics or commensal are defined as "Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Marco et al., 2021). In addition, age-related processes significantly reduce the diversity of intestinal microbiota due to the development of several disease such as cancers, frailty and neurological disorders (Bischoff, 2016). Human intestinal microbiota contains 500–1000 species and several million genera including commensal bacteria that are beneficial for the host due to their role against pathogens and improving the function of the immune system cells (Tuddenham & Sears, 2015). However, these beneficial probiotics could be reduced in numbers and functionalities due to bad food habits and processed diets. Commensal bacteria were extensively studied for their potential to positively modulate the immune system function via oral administration and colonization in the small intestines (Kabat, Srinivasan, & Maloy, 2014). LAB strains were reported to positively contribute to the immune system by forming barriers against viral infections. The probiotics antiviral mechanisms are still not well elucidated, thus Arena et al. (2018) suggested two mechanisms including the direct contact with the virus or indirect boosting of the host's immune system function.

Numerous *in vitro* and *in vivo* studies reported the potential antiviral activity of LAB towards broad range of alimentary and respiratory tracts viruses (Ang et al., 2016; Ermolenko et al., 2019; Jung et al., 2017; Seo, Jung, Jung, Yeo, & Choi, 2020). Certain LAB strains are known for their probiotics activity that can improve digestion system and suggested to have a protective effect against different subtypes of influenza A virus (Nakayama et al., 2014). Furthermore, LAB strains demonstrated broad range antiviral activity towards gastrointestinal viruses such as rotaviruses, noroviruses and enteroviruses (Atmar, Ramani, & Estes, 2018; Hu et al., 2018; Lukashev, Vakulenko, Turbabina, Deviatkin, & Drexler, 2018). They demonstrated indirect routes to prevent and/or reduce the symptoms of viral infections via improving the function of the immune cells. The consumption of high doses (10^9 CFU/mL) of probiotics was associated with rapid induction of IgG1 and IgG2a antibodies, induction of innate immune cells and cytokines (Jung et al., 2017). In addition, direct effect of the LAB was reported for down-regulation of influenza virus replication via induction of antiviral genes expression (Nakayama et al., 2014). In another study, the probiotic *Lactobacillus* isolated from *Kimchi* (fermented Korean vegetables) increased the induced NF- κ B and the production of pro-inflammatory cytokine achieved at dose-dependent intake (10^7 and 10^8 CFU/mL) (Jang, Yu, Lee, & Paik, 2020). The findings of the previous studies indicated that intake of probiotics should be regularly and at high dose (10^7 – 10^9 CFU/mL) to prevent viral infections. Therefore, this review will highlight the diversity of fermented foods, their probiotics and bioactive compounds. In addition, the interaction of these probiotics and bioactive compounds with the immune modulation activities that lead to viral prevention and fast recovery will be discussed.

2. Fermented foods

Fermented foods are those foods produced via back-slopping or spontaneous fermentation process that lead to conversion of raw materials into fermented products through enzymatic action of several microorganisms. Fermented foods are either animal-based or plant-based depending on the starting raw materials. Fermented dairy products (dairy products) are the earliest and most common animal-based fermented foods that have been consumed for thousands of years. However, the health benefits of fermented milk products such as cheese, yogurt, cultured milk, cultured cream, *leben* and *kefir* (Tamang et al., 2016), were realized for the first time in 1917 by Metchnikoff who described the health benefits associated with consuming fermented dairy products among certain populations in Eastern Europe (Anukam &

Reid, 2007). Traditionally, fermented dairy products prepared via natural fermentation depending on the presence of natural LAB in the raw milk. However, the traditional fermentation process cause safety issues in the fermented dairy products due to the potential growth of unwanted food-borne pathogens. Therefore, the process was improved using back-slopping as the raw milk is boiled to control the growth of microorganisms, while the starter culture is obtained from previous batch of dairy product (Groenenboom et al., 2019). Advancement in starter culture technology including the genome sequencing, selecting phage resistant strains and preservation techniques led to the application of customized starter cultures for fermented dairy products to control the quality and safety of the final products.

2.1. Animal-based fermented foods

Fermentation of meat was traditionally used to extend the shelf life of meat and to develop unique flavour in the new product. Fermented meat products with variation for the process and the additives are more common in Europe, North Africa, and United States (Chammem, Issaoui, De Almeida, & Delgado, 2018). The major microflora of fermented meat products belongs to the LAB especially the species *Lactobacillus* including *L. alimentarius*, *L. pentosus*, *L. plantarum*, *L. versmoldensis* followed by the species *Pediococcus* including *P. acidilactici* and *P. pentosaceus* (Tamang et al., 2016). The most well-known fermented meat products include fermented sausages, salami and jerky that can be prepared from beef, mutton and pork. *Basterma* (Arabic sausage) which is the most popular fermented minced beef in the Middle East in countries including Iraq, Syria, Lebanon, Egypt, and Jordan (Zaccheo, Palmaccio, Venable, Locarnini-Sciaroni, & Parisi, 2017). *Basterma* is prepared via natural fermentation by mixing the minced meat with garlic, salt and seasonings that is stuffed in cow intestines and kept at room temperature for 7–14 days. In Vietnam, *Nem chua* is very popular fermented ground lean pork prepared with different spices and incubated at room temperature for 3–4 days and LAB are the dominant microorganisms found in the final product (Nguyen et al., 2010). Moreover, fermented fish and fish sauce prepared via spontaneous fermentation process are well known in Asian countries including China, Japan, Malaysia, Indonesia, Thailand, and Philippine. The fermentation is not only to preserve the fish, but also to ensure the absence of pathogenic microbes. The fermentation process involves great diversity of microorganisms that are naturally found on the surface of the fish and in the gut and stomach linings (Legrand, Wynne, Weyrich, & Oxley, 2020). *Belacan* or *kapi* is shrimp paste that is spontaneously fermented in the presence of salt and the natural microflora of shrimps (Lv et al., 2020). *Budu* is a brown fish sauce found in Malaysian and produced by mixing certain types of fish such as *Stolephorus* spp. and *Sardinella* spp with salt and spontaneously fermented (Mohamed, Man, Mustafa, & Manap, 2012). *Budu* is known with many names in Asian countries including *nam pla* in Thailand, *patis* in Philippines, *terasi* in Indonesia, *teuk trei* in Cambodia and *nước mắm* in Vietnam. Aquatic-based fermented foods prepared based on spontaneous fermentation due to the presence of broad range microflora on their surface. However, the application of starter cultures was recommended to ensure the safety of the products from pathogenic bacteria due to the production of antimicrobial compounds such as organic acids, fatty acids, bacteriocins and bioactive peptides (Kumar et al., 2017).

On the other hand, fermented milk products are more common in the diets in Europe, North America, Middle East and North Africa (Tamang et al., 2020). Thus, some products are found in Asian countries such as *dadiah* in Indonesia *dahi* in India and *kumis* in Mongolia (Tesfaye, Suarez-Lepe, Loira, Palomero, & Morata, 2019). The fermented milk products involve a large diversity of microorganisms including bacteria, yeast and fungi (Wouters, Ayad, Hugenholtz, & Smit, 2002). Cultured milk is a very popular product prepared via spontaneous fermentation of cow or sheep milk (Delgado et al., 2013). Yogurt is the simplest fermented milk product that is produced using two established LAB strains

namely *L. delbrueckii* subsp. *Bulgarius* and *Streptococcus thermophilus* (Delavenne et al., 2013). Cheese is an ancient fermented milk product with approximately 1400 varieties fall in this category (McSweeney, Ottogalli, & Fox, 2004). Different cheese types are produced using different starter cultures such as bacteria (Majorero, Pecorino Siciliano, Feta), yeast (Parmesan, Cheddar, Romano, Gouda) and fungi (Gruyere, Monterey Jack, blue cheese) (Banjara, Suhr, & Hallen-Adams, 2015; Settanni & Moschetti, 2010). However, LAB is the dominant microflora of milk fermented products and their main function is to utilize the lactose and produce lactic acid (Muhialdin & Alboory, 2018). Traditional fermented milk products are a rich source of bioactive compounds including peptides, amino acids, vitamins, and minerals (Santiago-López et al., 2018).

2.2. Plant-based fermented foods

Plant-based fermented foods including fermented cereals and legumes, vegetables and fruits are rapidly growing due several factors including the low cost of raw materials, diversity of the raw materials and the claims of health benefits. In addition, the high demands from vegetarians and vegans have led to the increase in the innovation for plant-based fermented foods. Plant-based fermented foods are abundant in Asian countries such as fermented glutinous rice (*tapai pulut*) and tapioca (*tapai ubi*) in Malaysia, *dosa* in India, *kimchi* in South Korea and *natto* in Japan (Ray, Ghosh, Singh, & Mondal, 2016; Merican & Quee-Lan, 2004). Legume-based fermented foods are mainly those of soybean (*Glycine max*), black gram (*Vigna mungo*), chickpea (*Cicer arietinum*) and mung beans (*Vigna radiata*) (Adebo et al., 2017). Soybean is extensively used for the preparation of fermented foods including *doenjang*, *doubanjiang*, *miso*, *natto* and *tempeh*. Their main differences are the fermentation process, additives and microorganisms. Fermented vegetables include broad range of raw materials such as pepper, cucumber, cabbage, radish, mustard, onion, ginger and olives (Tamang et al., 2016). However, *Kimchi* from Korea and *sauerkraut* from German are globally recognized vegetable-based fermented foods prepared using cabbage with unique fermentation process for each product (Patra, Das, Paramithiotis, & Shin, 2016). *Kimchi* is prepared by slicing the cabbage into small pieces and adding 7%–15% salt to reduce the water content and establish conditions for the growth of desirable microorganisms. The processed cabbage is packed in the final containers and kept at 28 ± 2 °C for 2–3 days. On the other hand, *sauerkraut* is prepared by shredding the cabbage into very small strips and mixed with salt (1%–5%) and fermented at 15 °C for 2–3 days (Palani et al., 2016). *Kimchi* and *sauerkraut* were proposed as functional foods the was supported by several *in vitro* and *in vivo* studies to have broad range functionality such as anticancer, anticonstipation, antiobesity and improve immune system function (Peñas, Martínez-Villaluenga, & Frias, 2017; Park, Jeong, Lee, & Daily III, 2014). The functional properties were found to be in correlation with the natural microflora mainly probiotics and the bioactive compounds such as the phenolic compounds, vitamins, amino acids, and peptides. On the other hand, fermented plant-based beverages such as vinegar (Samad, Azlan, & Ismail, 2016), and kombucha (fermented sugared tea) (Chakravorty et al., 2016) have very well documented preparation methods and health benefits. Vinegars are made using variety of fruits such as date, apple and grape. Their health benefits including antioxidant, antimicrobial, antihypertensive, antidiabetic and antiobesity were recently well documented (Ho, Lazim, Fazry, Zaki, & Lim, 2017). On the other hand, kombucha is an ancient beverage made from sugared tea using symbiotic culture of bacteria and yeast (SCOBY) (Chakravorty et al., 2016). It is health benefits include antioxidant (Muhialdin et al., 2019), anticancer (Villarreal-Soto et al., 2019), antimicrobial (Tan, Muhialdin, & Meor Hussin, 2020). Plant-based fermented foods and beverages are regularly consumed in Asia and Africa with less frequent at the Western countries where milk-based fermented foods are dominant (Tamang et al., 2020). However, the increased awareness regarding their health benefits alongside the recent Covid-19

pandemic have led to increase the demand for the plant-based fermented foods and beverages (Antunes, Vinderola, Xavier-Santos, & Sivieri, 2020).

3. Potential health benefits of animal-based and plant-based fermented foods

Fermentation improves taste and aroma of the animal-based and plant-based raw materials. In addition, fermented foods have long been thought to provide health benefits to the consumer. Fermented foods enhance probiotic bacteria content and consequently augment of metabolic functions needed and available to the gut for building resilience in a healthy individual. The potential health benefits of fermented foods that have been explored in recent studies were based on an extensive body of anecdotal information, and included such benefits as: antihypertensive activity (Ahrén et al., 2015; Koyama, Hattori, Amano, Watanabe, & Nakamura, 2014; Nakamura, Naramoto, & Koyama, 2013), blood glucose-lowering benefits (Kamiya, Ogasawara, Arakawa, & Hagimori, 2013; Oh et al., 2014), anti-diarrheal (Parvez, Malik, Ah Kang, & Kim, 2006), and antithrombotic properties (Kamiya et al., 2013). The health benefits of fermented foods suggested being due to direct and indirect routes (Mota de Carvalho et al., 2018). Their direct route of action is attributed to different bioactive compounds which were produced during the fermentation that are not naturally found in their unprocessed counterparts such as fatty acids, organic acids, vitamins, bacteriocins, amino acids, peptides and exopolysaccharides (Mapelli-Brahm et al., 2020; Adesulu-Dahunsi, Jeyaram, & Sanni, 2018). The health and disease prevention effect of fermented food are due to increased production of bioactive compounds such as polyphenols, bioactive peptides, conjugated linoleic acid, gamma amino butyric acid and vitamins (Hayes & García-Vaquero, 2016, pp. 293–310). The bioactive compounds are from two different sources including the compounds released from the raw materials due to the high acidity and hydrolysis enzymes from the microflora and/or produced by the friendly microorganisms (probiotics) (Adebo & Gabriela Medina-Meza, 2020).

Animal-based fermented foods are usually associated with health-promoting components with antioxidant, anti-radical, anti-hypertensive activity and alleviation of lactose intolerance that are partly or mainly resulted by the activities of bioactive peptides and short chains fatty acids (SCFAs) produced or released by fermentation of milk or meat products shown in Table 1. One of the most common bioactive peptides that are produced by fermented milk, meat and clams is the angiotensin-converting enzyme inhibitory (ACE-I) peptides (Chen et al., 2015; Izquierdo-González et al., 2019; Rai, Sanjukta, & Jeyaram, 2017). ACE-I peptides in *Lactobacillus* fermented milk are associated with anti-hypertensive effect due to the reduced angiotensin formation (Gonzalez-Gonzalez, Gibson, & Jauregi, 2013; Wang et al., 2015). Other bioactivities reported includes antimicrobial, antihemolytic, anti-mutagenic, and anti-inflammatory effects (Muhialdin, Alboory, et al., 2020). Dry-fermented Spanish sausage was reported to release ACE-I, antioxidative, antimicrobial, immunomodulating and antithrombotic activities when *L. pentosus* and *Staphylococcus carnosus* were used as a starter culture (Mora, Escudero, Aristoy, & Toldrá, 2015). Another study by Chen et al. (2018) reported the production of a peptide with high ACE-1 activity when *Ruditapes philippinarum* clams was fermented with *Bacillus natto* which also exerts anti-cancer property. Other than ACE-I production, SCFAs production during human gut microbiota fermentation was discovered by Pérez-Díaz (2019) when investigating the potential health effects of probiotic salami with dietary fibre. According to Bartkiene et al. (2019), lacto-fermentation can enhance the safety and nutritional value of fermented meat products due to the production of several antimicrobial compounds and the degradation of toxins naturally present in meat. Meat toxins that can cause serious health risk including polycyclic aromatic hydrocarbons (PAH) and biogenic amines (BA) were reported to be significantly decreased during the

Table 1
Fermented foods, their health benefits, substrates and the associated probiotic bacteria.

Substrate	Fermented foods	Health benefits	Associated probiotics	References
Animal-based				
Cow milk	Fermented milk	Angiotensin I-converting enzyme (ACE) inhibitory activity.	<i>Bifidobacterium bifidum</i> MF20/5	Gonzalez-Gonzalez et al. (2013)
Cow milk, mare milk	Fermented milk	ACE inhibitory activity.	<i>Lactobacillus helveticus</i>	Wang et al. (2015)
Cow milk	Fermented milk	Anti-inflammatory, antihemolytic and antioxidant activity.	<i>Lactobacillus plantarum</i>	Aguilar-Toalá et al. (2017)
Pork Meat	Dry-fermented sausages	ACE inhibitory, antimicrobial and immunoregulatory activity.	Lactic acid bacteria	Mora et al. (2015)
Marine bivalve (<i>Ruditapes philippinarum</i>)	Fermented bivalve	ACE inhibitory activity, anti-hypertension and antioxidant effect <i>in vitro</i> .	<i>Bacillus natto</i>	Chen et al. (2018)
Plant-based				
Rice bran	Fermented rice bran	Reduce growth of human lymphoma <i>in vitro</i> .	<i>Saccharomyces boulardii</i>	Ryan (2011)
Fhu Zhuan leaves	Fu Zhuan tea	Anti-obesity, anti-microbial activity.	<i>Eurotium cristatum</i>	Kang et al. (2019), Keller et al. (2013)
Red ginseng roots	Fermented red ginseng roots	Anti-diabetic properties.	<i>Lactobacillus plantarum</i>	Oh et al. (2014)
Hydroponic ginseng	Fermented hydroponic ginseng	Antioxidant, anti-inflammatory and anti-adipogenic properties.	<i>Leuconostoc mesenteroids</i> KCCM	Hwang et al. (2019)
Soybean	Chunghookjang	Antidiabetic properties of bioactive peptides.	<i>B. licheniformis</i> B1	Yang et al. (2013)
Soybean	Douchi	ACE inhibitory effect of bioactive peptides.	<i>A. aegypticus</i>	Zhang, Tatsumi, Ding, and Li (2006)
Soybean	Korean soybean paste	ACE inhibitory effect of bioactive peptides.	Not specified	Shin et al. (2001)
Cabbage	<i>Kimchi</i>	Probiotic ability <i>in vitro</i> .	<i>L. plantarum</i> Ln4	Son et al. (2017)
		Probiotic ability and antimicrobial activity <i>in vitro</i> .	<i>L. brevis</i> KU15153	Jang et al. (2020)
		Probiotic ability and antioxidant activity <i>in vitro</i> .	<i>L. brevis</i> B13-2	Chung et al. (2020)
		Probiotic ability, antioxidant activity and lipid oxidation inhibition ability <i>in vitro</i> .	<i>L. brevis</i> KCCM 12203P	Song et al. (2020)
		Probiotic ability, anti-microbial, anti-inflammatory, antioxidant activities and anti-cancer effect.	<i>L. lactis</i> KC24	Lee et al. (2015)
Rice and black gram	<i>Idli</i>	Probiotic ability <i>in vitro</i> .	<i>Bacillus</i> spp.	Shivangi, Devi, Ragul, and Shetty (2020)
Wheat flour dough	<i>Babroo</i>	Probiotic ability and antioxidant activity <i>in vitro</i> .	<i>L. fermentum</i> , <i>L. plantarum</i> , <i>acidilactici</i>	Sharma, Attri, & Goel, (2019)
Curly cabbage	Sauerkraut	Probiotic ability	<i>L. plantarum</i> 332, <i>L. paraplantarum</i> G2114, <i>L. brevis</i> R413, <i>L. curvatus</i> 154	Michalak, Gustaw, Waško, and Polak-Berecka (2018)

fermentation using LAB starter cultures (Laranjo, Potes, & Elias, 2019).

Health-promoting components with anti-cancer, antioxidant, anti-hypertensive, anti-diabetic and anti-microbial activities can be derived from fermented plant-based products with plant bioactive compounds that are produced through pre-treatment of raw materials by fermentation or by applying fermentation to the whole food system production (Melini et al., 2019). Some examples of fermented plants and the probiotic microorganisms which contributes to the many health benefits are highlighted in Table 1. Fermented rice bran was discovered to have anti-cancer properties. In a study using different rice (*Oryza sativa*) cultivars, rice bran fractions were fermented by *Saccharomyces boulardii*, and each of the three fermented rice brans showed significant differences in metabolite composition compared to non-fermented (Ryan, 2011). In this study, the rice brans found to have different profile of phytochemicals and therefore the bioactive compounds profile was different for the fermented rice bran.

Fu Zhuan (*Camellia sinensis*) tea is a fermented beverage product which has been discovered to have anti-obesity and anti-microbial properties (Kang, Su, Duan, & Huang, 2019; Keller, Weir, Broeckling, & Ryan, 2013). Tea leaves were fermented with the fungus *Eurotium cristatum* and showed increased amounts of dodecanamide, linoleamide, stearamide, and epicatechin gallate when compared to a non-fermented tea (Keller et al., 2013). Ginseng roots represent another plant containing bioactive compounds including saponins (ginsenosides) and nonsaponins, with as many as 50 ginsenosides identified to date that provide potential benefits to regulation of blood glucose and insulin levels (Oh et al., 2014). Fermentation of the ginseng roots has been demonstrated to increase the content of saponins naturally found in the plant and was found to exhibit anti-diabetic, antioxidant, anti-inflammatory and anti-adipogenic properties (Oh et al., 2014;

Hwang, Kim, & Paik, 2019). Fermented food products using soybean as the substrate such as, *chunghookjang*, *douche* and Korean soybean paste have also been found to produce bioactive peptides which leads to health benefits such as anti-diabetic and ACE inhibitory activities. Other traditionally fermented foods such as the *kimchi*, *idli*, *babroo* and sauerkraut have also been proven to have probiotic, antioxidant and antimicrobial properties (Table 1). Critical functions for microbes associated with plant-based foods include the contribution to improve the defence activities of the human host. Fermentation serves to pre-adapt beneficial microbes indigenous to fresh vegetables to the acidic pH and high lactic acid concentration characteristic of the colon and to the metabolism of dietary fibre, particularly pectic substances naturally present in the plant material and the gut (Pérez-Díaz, 2019). The great numbers of studies found in the literature demonstrated the health benefits of plant-based and animal-based fermented foods (Chilton, Burton, & Reid, 2015; Marco et al., 2017, 2021; Tamang et al., 2016). The health benefits of fermented foods are associated with the bioactive compounds that are not present or present at low concentration in the starting raw materials (Muhiyaldin, Hussin, Kadum, Hamid, & Jaafar, 2021; Villarreal-Soto et al., 2019). Therefore, the selection of the raw materials and the starter cultures are very critical for the production of bioactive compounds with certain health benefits. Thus, the modification of the fermentation process should not have or have minimal effect on the consumer preference especially for the traditional fermented foods and beverages.

4. Fermented foods probiotics/active components and the immune system

The immune system is the key player to prevent the invasion of

viruses at the early stage of the infections. Boosting and stimulating the immune system is one of the strategies to prevent infections caused by different pathogens including viruses (Vald'es, Lazo, Hermida, Guillen, & Gil González, 2019). The human immune system composed of two major parts including the innate immune system (fast non-specific response system) and adaptive immune system (slow specific response system). The innate and adaptive immune cells demonstrate important series of events that lead to prevention or recovering from infections. Innate immune is the first protection line against pathogenic infections that enter the body, and their fast response is to eliminate these pathogens by direct demolition (Murray & Wynn, 2011). The innate immune consists of macrophages, neutrophils, eosinophils, natural killer cells, epithelial cells and M cells (Germic, Frangez, Yousefi, & Simon, 2019). In addition, innate immune cells that excrete several cytokines including type I interferon (IFN) and interleukins IL-1, IL-6, IL-12, and IL-16 and they have very important functions in combatting several infections caused by pathogens and viruses (Akdis et al., 2016). On the other hand, the memory B cells, and memory T cells are the most important cells for the functions of adaptive immune system.

Several studies reported that probiotics isolated from different fermented foods improved the immune cells function of the host (Table 2). According to Nishihira et al. (2018), the molecular mechanism of the probiotics to enhance the immune system response is via the interaction

Table 2

In vitro and *In vivo* studies of fermented foods consumption and the enhancement of immune function.

Fermented food	Microbes present	Immune response	Reference
Fermented soybean	LAB	Enhance splenic natural killers cell activity	Lee et al. (2017)
Fermented fruits and vegetables Xeniji	LAB mixed with yeast	Enhanced immunity function	Zulkawi et al. (2017)
Fermented Maillard-reactive whey protein	<i>L. plantarum</i> LC01	Enhanced natural killers cell function	Kang et al. (2017)
Yogurt	<i>L. delbrueckii</i> ssp. <i>bulgaricus</i> , <i>Streptococcus thermophilus</i> and <i>L. casei</i> DN 114 001	Stimulated production of pro-inflammatory cytokines	Meyer, Elmadfa, Herbacek, and Micksche (2007)
Yogurt	<i>L. delbrueckii</i> ssp. <i>bulgaricus</i> , <i>Streptococcus thermophilus</i> and <i>L. casei</i> DN 114 001	Increase cytotoxic T lymphocytes (CD3 ⁺ CD16 ⁺ CD56 ⁺)	Meyer et al. (2006)
Yogurt	<i>L. delbrueckii</i> ssp. <i>bulgaricus</i> , and <i>Streptococcus thermophilus</i>	Increase of IFN-gamma production	Solis et al. (2002)
Oligosaccharide-enriched low-fat milk.	<i>Bifidobacterium lactis</i> HN019	Enhanced phagocytosis and NK cell tumour killing activity	Chiang, Sheih, Wang, Liao, and Gill (2000)
Fermented milk	<i>L. casei</i> Shirota	Enhanced natural killers cells function	Nagao, Suzui, Takeda, Yagita, and Okumura (2000)
Fermented milk	<i>L. casei</i> and <i>L. acidophilus</i>	Prevent pathogens growth	Perdigon, Vintini, Alvarez, Medina, and Medici (1999)
Fermented milk	<i>L. acidophilus</i>	Enhance phagocytosis against <i>E. coli</i> ssp.	Schiffirin, Brassart, Servin, Rochat, and Donnet-Hughes (1997)

with epithelial cells, dendritic cells, and T-cells that lead to the induction of several cytokines including TGF- β , IL-6, IL-10. The immune system response was found to be improved in correlation with the bioactive compounds generated by the probiotics in the fermented foods such as extracellular polysaccharides, bacteriocins and butyric acid (Li & Gänzle, 2020; Ermolenko et al., 2019; Van Immerseel et al., 2010). In previous study, dextran which is an extracellular polysaccharide synthesised by certain probiotic strains demonstrated antiviral effects against Infectious hematopoietic necrosis virus (Nácher-Vázquez et al., 2015). The researcher suggested that the mechanism was a direct interaction between the virus cellular surface and dextran which lead to inhibition of the virus replication cycle. In another study, the effects of the surface exopolysaccharides (EPS) biosynthesised by *Bifidobacterium breve* UCC2003 on the immune response were evaluated in *in vivo* study. The findings indicated significant elevated levels of pro-inflammatory cytokines including IFN- γ , TNF- α , and IL-12 as a result of the pre-treatment with the EPS. The immune system response mechanism was due to the influence of EPS on the adaptive immune cells including B-cells and T-cells (Fanning et al., 2012). On the other hand, consumption of fermented foods and probiotics are being used as novel method to enhance the function of the innate immune system especially Natural Killer Cells (NKC) and reduced the intestinal inflammatory diseases (Fig. 1). Natural killer cells are part of the innate immune system and play important role in the protection of the body against antigens. They are the first defence line against any foreign infections and inner tumour formation, and they attack microbes directly without the need for stimulators like other types of immune system cells (Vivier et al., 2011). Moreover, fermented foods and their probiotics were observed to improve the gut microbiota to the favour of health microorganisms including those belong to the genus *Lactobacillus* and *Bifidobacteria* (Pasolli et al., 2020; Sanders, Merenstein, Reid, Gibson, & Rastall, 2019). The gut microbiota plays very important role to boost the immune system due to their functions including the detoxification of toxins, production of antibodies, enhance NKC cytotoxicity, reduce inflammations and prevent the colonization of enteropathogenic (Ashaolu et al., 2020). Fermented foods are rich source of bioavailable nutrients that will provide the building blocks for producing new immune cells by the specialised organs (Oliphant & Allen-Vercoe, 2019).

Balanced nutrients are directly related to the status of the immune system function for individuals. In addition to the Immune Deficiencies Diseases (IDD), insufficient intakes of macronutrients largely reduce the immune system response to infections. According to Calder and Kew (2002) all types of immunity cells are affected by limited intakes of one or more of these nutrients including essential amino acids, the essential fatty acid linoleic acid, vitamin A, folic acid, vitamin B6, vitamin B12, vitamin C, vitamin E, Zn, Cu, Fe and Se. Healthy human usually have sufficient innate immune component but is not the same for certain groups such as infants, the elderly, immune deficient diseases, stressed individuals, and patients undergoing surgery, these groups are at high risk of infections due to temporary or permanent destabilized immune function (Gill, 1998). However, the potential health benefits of fermented foods are limited to the prevention of viral infections and the reduction of symptoms (Olaimat et al., 2020). Fermented foods and their bioactive compounds were suggested to be combined with conventional therapy to reduce the hospitalization period for the patients (Rocks et al., 2020).

5. Consumption of fermented foods for their antiviral activity

Viral entry to the human body and the development of infections involve several steps including the attachment of the virion to the cell surface and the delivery of the viral genome to the site of replication. Thus, the most important step for virus entry is to penetrate through the cellular membrane (Helenius, 2018). The most common routes for viral infections are respiratory and alimentary tracts. The ventilation rate for the human is equal to 6 L of air/minute that lead to the entry of great

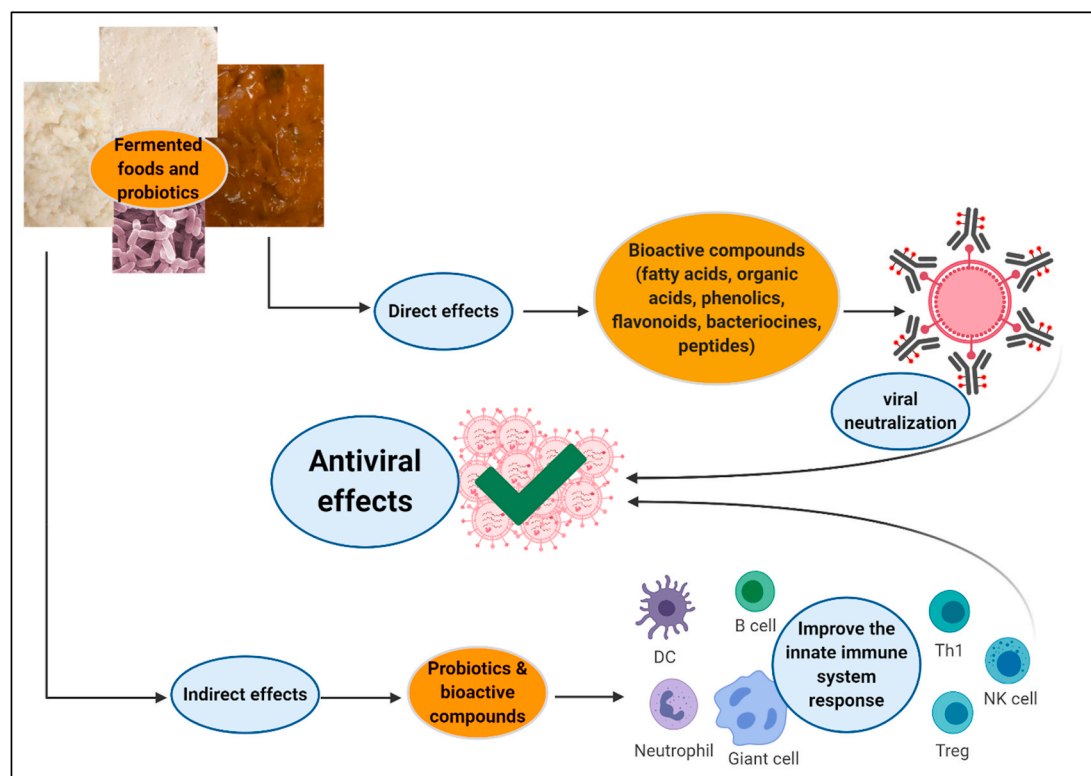


Fig. 1. The role of the fermented food and their bioactive compounds in improving the immune system function and prevention of viral infections.

numbers of foreign particles and viruses. On the other hand, daily voluntary activities such as eating, and drinking may introduce viruses to the alimentary tract. However, virus entry requires several factors such as presence of sufficient viral genome, accessibility to the infection site and the absence of the immune system response (Doms, 2016).

The human body has several defence mechanisms to prevent the entry of viruses that can cause respiratory tract infection. The respiratory tract mechanical barriers lined with a mucociliary blanket consisting of ciliated cells, mucous-secreting goblet cells, and sub-epithelial mucous-secreting glands. The viruses entering through the nasal cavity or upper respiratory tract will be trapped in mucus, carried to the back of the throat, and swallowed. Moreover, the ciliary action in the lower respiratory tract play important role to remove any particles trapped in the lung mucus to the throat (Gizurason, 2015). The lowest portions of the respiratory tract contain macrophages coating the alveoli ingest and destroy particles including viruses (He et al., 2017). On the other hand, the alimentary tract is naturally protected due to the secretion of pH, protease enzymes, and bile detergents that can prevent the entry of viruses and prevent infections (Doms, 2016). Thus, certain viruses such as enteric coronaviruses can survive the harsh conditions in the alimentary tract, but their survival mechanism is not fully understood. The enteric viruses with robust resistance to the digestive system condition are of important concern in the foods supply chain due to their serious health threats to the consumers (Miranda & Schaffner, 2019). However, LAB is the dominant microbial community in fermented foods and viruses belong to the family Microviridae present at low concentration and represent low risk for the consumers (Jung et al., 2018).

Vaccination is the most established strategy to prevent viral infections via inducing strain-specific immune responses to targeted strains (Lee, Lee, Kim, Gewirtz, & Kang, 2016). However, viral infections consist of a broader range of virus subtypes that are not recognized by the long-term immune response (Wolfe et al., 2017). The life cycle of viruses including their attachment, replication and separation is totally carried out inside the host cells cytoplasm (Chahar, Bao, & Casola, 2015). Therefore, several antiviral drugs have been developed to disturb

and inhibit the virus life cycle to prevent infections. Drugs targeting viral enzymes including polymerase, protease and integrase are the most common antiviral agents. Another group of antiviral drugs targets the viral proteins and/or host cell factors to inhibit viral replication inside the cells (Heylen, Neyts, & Jochmans, 2017). Nitazoxanide reported to have high anti-influenza potential by interfering with the maturation of viral hemagglutinin at a post-translational stage and blocking viral replication (McKimm-Breschkin et al., 2018). In addition, certain drugs such as MBX-300 can interact with the host receptors and prevent viral attachment by blocking the electrostatic binding to the cell membrane (Kimura et al., 2000). However, antiviral drugs have side effects including nausea and diarrhoea, and can lead to serious side effects such as kidney problems and liver injury (Fang, Qi, Zhou, & Li, 2018). Furthermore, the excessive use of antiviral drugs caused emerging of virus resistance due to mutations (Mason, Devincenzo, Toovey, Wu, & Whitley, 2018). Therefore, high demand observed for non-conventional antiviral agents that can reduce the risk and severity of viral infections. Recently, probiotic bacteria were extensively investigated for their broad range of antiviral activity. Majority of probiotics belong to lactic acid bacteria (LAB) group with generally regarded as safe (GRAS) status and immunomodulatory actions (Mojgani, Shahali, & Dadar, 2020). These probiotics are high abundant in several traditional fermented foods of plant-based or animal-based origins (Zhao et al., 2019). In addition, the probiotics with broad range antimicrobial activity was suggested to be included in the traditional fermented foods to enhance their functionality including the antiviral activity (Marco et al., 2021).

6. Antiviral activity of fermented foods and their probiotics

The antiviral activity of fermented foods and their probiotics was suggested to be due to their capacity to stimulate the host immune system response against viral infections (Hardy, Harris, Lyon, Beal, & Foey, 2013). On the other hand, the bioactive compounds in the fermented foods that is generated by the probiotics bacteria play an important role to enhance the antiviral activity. Therefore, due to their

antiviral activity, the probiotics have been renamed to “Immunobiotics” (Villena, Vizoso-Pinto, & Kitazawa, 2016). Lactobacilli which is a major genus of probiotics were found to stimulate immune response by increasing phagocytic activity, plasma lysozyme, complement activation and enhancing the production of superoxide anion (Harikrishnan, Balasundaram, & Heo, 2010). The antiviral activity of several probiotics was reported against respiratory and alimentary tracts viruses (Table 3). The mechanism of antiviral activity is not very clear whether it is due to the probiotic cells, their bioactive compounds and/or the mixture of cells and bioactive compounds. The antiviral mechanism of fermented foods is not well known due to the limited clinical studies documented the daily intake for long term (Aslam et al., 2020). On the other hand, the mechanism of probiotics has been established via several well designed clinical studies that recommended the required doses per day (Rozga, M., Cheng, F. W., & Handu, 2020; King, Glanville, Sanders, Fitzgerald, & Varley, 2014; Reid, Jass, Sebulsky, & McCormick, 2003). Influenza virus is one of the common viruses that can cause serious respiratory tract infection and lead to high morbidity and mortality especially during influenza epidemics (Taubenberger & Morens, 2008). Therefore, numerous studies were carried out to evaluate the potential antiviral activity of several probiotic strains isolated from fermented foods against influenza virus and its subtypes. Jung et al. (2017) reported the antiviral activity of the probiotic strain *L. casei* DK128 isolated from kimchi against influenza H3N2 virus. The *in vivo* results demonstrated complete survival of the mice subjected to high lethal infection with H3N2 virus and treated different doses of the probiotic including log 7, log 8 and log 9 CFU mL⁻¹. However, the mice group treated with log 9 CFU mL⁻¹ showed no weight loss compared to log 7 and log 8 CFU mL⁻¹ that exhibited 10%–12% weight loss.

Clinical trial using yoghurt containing *L. lactis* in a study group, and placebo beverage in control group showed significant reduction in influenza like symptoms in the study group compared to the control group in winter season. The peripheral blood mononuclear cells was cultured with inactivated human influenza virus A (H1N1) showed remarkable increase in interferon alpha (IFN- α), IFN- α inducible antiviral factor and interferon stimulated gene in the study group compared to the control (Sugimura et al., 2015). Bacteriocins produced from the LAB named *E. durans* was found to inhibit viral replication of herpes

simplex virus 1 and poliovirus *in vitro* making it to be a potential antiviral agent (Cavicchioli et al., 2018). The heat killed *L. plantarum* (Nfl) was found to reduce mortality rate in mouse models infected with influenza type A (H1N1 and H3N2 subtypes) and Influenza B (Yamagata Lineage). The authors suggested the strain as a possible alternative to influenza vaccine especially in resource poor settings (Park et al., 2013). Kawashima et al. (2011) reported the antiviral activity of *L. plantarum* YU isolated from Japanese fermented foods with the ability to reduce the replication of influenza A virus due to the enhancement of Th1 immune responses. In another study, the probiotic strain *L. plantarum* DK119 isolated from kimchi (fermented cabbage) demonstrated 100% protection against influenza A viruses (Park et al., 2013). High levels of cytokines IL-12 and IFN- γ were detected in broncho-alveolar lavage fluids of the treated mice which indicate modulating of the host innate immune system.

The recent Covid-19 pandemic has attracted the attention of physicians for the potential antiviral effects of fermented foods and probiotics due to the absence of any prevention or treatment protocols (Baud, Dimopoulou Agri, Gibson, Reid, & Giannoni, 2020). On the other hand, several researchers proposed the potential of fermented foods that have diversity of probiotics to be used as strategy to boost the immune system and reduce the fatality and duration for recovery (Antunes et al., 2020). Covid-19 infection was found to alter the gut microbiota of the patients despite their age and the clinical results showed significant increase in pathogenic communities over the friendly bacteria (Zuo et al., 2020). The increase in the pathogenic communities will stress the immune system and significantly reduce its function in the face of the Covid-19 (Shook, Sevi, Lee, Oosterhoff, & Fitzgerald, 2020). Therefore, the consumption of fermented foods and probiotics can restore and balance the gut microbiota via introducing the friendly bacteria leading to reduce the immune system stress and boost its function against the viral infection (Bousquet et al., 2020a).

The term human microbiota refers to the set of microorganisms that we host as human beings. In another study, Bousquet et al. (2020b) suggested that the low death rate caused by Covid-19 in Asia, Africa, Eastern Europe and Middle East is due to their diet that contain broad range of fermented foods. Majority of these traditional fermented foods contain high amounts of probiotics belong mainly to the genus

Table 3

Antiviral activity of the probiotic bacteria isolated from different fermented foods and their mechanism towards different viruses.

Strain	Source	Targeted virus	Testing method	Mechanism	Reference
<i>Pediococcus pentosaceus</i> (CAU170229-2 and CAU170230-3), <i>Weissella cibaria</i> (CAU170231-1 and CAU170231-3)	Kimchi (Korean fermented cabbage)	Murine norovirus	<i>In vitro</i> (RAW264.7 cells)	Stimulating NF- κ B, IL-1 β , TNF- α , and NO in macrophages	Seo et al. (2020)
<i>Enterococcus faecium</i> L3	Dairy product	Influenza virus (H3N2, H1N1)	<i>In vitro</i> (MDCK cell line), <i>in vivo</i> (female Balb/c mice)	Enterocin B may stimulate interferon production and to enhance the humoral immune response	Ermolenko et al. (2019)
<i>L. casei</i> DK128	Kimchi (Korean fermented cabbage)	Influenza virus (H1N1, H3N2)	<i>In vivo</i> (Female BALB/c mice, C57BL/6 mice)	Rapid induction of IgG1 and IgG2a antibodies, induction of innate immune cells and cytokines	Jung et al. (2017)
<i>L. reuteri</i> ATCC 55730	Human stomach	Coxsackieviruses CA6, CA16 and Enterovirus 71	<i>In vitro</i> (skeletal muscle RD, intestinal Caco-2 cells)	Modulation of inflammatory cytokines and chemokines production	Ang et al. (2016)
<i>L. gasseri</i> SBT2055	Human faeces	Influenza virus (A/PR8)	<i>In vivo</i> (Male C57BL/6N mice)	Down-regulation of viral replication via the induction of antiviral genes expression	Nakayama et al. (2014)
<i>L. plantarum</i> DK119	Kimchi (Korean fermented cabbage)	Influenza A virus (A/PR8)	<i>In vivo</i> (Female BALB/c mice)	Enhance the levels of cytokines IL-12 and IFN- γ	Park et al. (2013)
<i>L. plantarum</i> YU	Japanese fermented food	Influenza A virus (A/NWS/33, H1N1)	<i>In vivo</i> (Female BALB/c mice)	Inducing IL-12 and IgA, enhancement of Th1 immune responses	Kawashima et al. (2011)
<i>L. acidophilus</i> , <i>L. rhamnosus</i> , <i>L. plantarum</i> , <i>Streptococcus thermophilus</i> and <i>Bifidobacterium bifidum</i>	Yogurt	Enteroviruses, Influenza virus (A/PR/8/34), influenza virus (B/Lee/40)	<i>In vitro</i> (MDCK and Vero cells)		Choi, Song, Ahn, Baek, and Kwon (2009)

Lactobacilli and their consumption is associated with health benefits and well-being status. However, there are no pre-clinical or clinical studies published to support the hypothesis for using fermented foods and probiotics for treatment protocols against Covid-19.

Several studies showed the high potential for probiotics as antiviral agents against alimentary viruses such as rotaviruses (Hu et al., 2018), noroviruses (Atmar et al., 2018) and enteroviruses (Lukashev et al., 2018). The alimentary tract is naturally protected by the low pH, and secretion of protease enzymes and bile detergents which can destroy viruses before the attachment and fusion to the host cells (Doms, 2016). Thus, some viruses are susceptible to these conditions and can cause alimentary tract infections. Several studies reported the high potential of certain probiotics to disturb these viruses at early stage. Probiotics have higher antiviral potential towards alimentary tract viruses due to the direct contact at the intestinal lumen (Karst, 2016). *L. ruminis* and *Bifidobacterium longum* SPM1205, and SPM1206 probiotic strains were found to have antiviral activity against human rotavirus infection as determined using Caco-2 cells. In addition, the probiotic strains inhibited the replication of the virus in neonatal mouse model. The antiviral effects was suggested to be mediated by activating type I Interferons which induced antiviral effectors (Kang, Lee, Ha, & Shin, 2015). In another study, *Bifidobacterium adolescentis* was found to prevent the multiplication of Murine norovirus-1 (MNV-1) *in vitro* after been cultured together on RAW 264.7 cells. The probiotic strain inhibited the binding of virus like particles (VLPs) of the Norovirus (NoV) to Caco-2 cells and HT-29 cells (Li, Breiman, Le Pendu, & Uyttendaele, 2016). Moreover, clinical trials showed that certain probiotics increased the production and secretion of IgA in mucosal cells by IL-6 and IL-10 as a result of stimulation of the dendritic cells. The antigen specific IgA was found to prevent attachment and invasion of mucosal membranes by viruses (Kawashima et al., 2018). The bioactive compounds produced by the probiotics such as lipopolysaccharides (LPS) were found to be very important to prevent viruses attachment to the host cells (Robinson, Jesudhasan, & Pfeiffer, 2014). The results of the previous studies demonstrated the promising role for probiotics to prevent viral infections or reduce the severity of the symptoms. Therefore, there is a high potential to use probiotics in combination with conventional treatment will have the potential to enhance the immune system function and reduce the hospitalization period.

7. Direction for future research

Diets are responsible for building the host immune system to be highly functional and efficient in responding to viral infections. Thus, a balanced diet for the host from early life stage may have significant impact on the host intestinal microbiota. Moreover, intestinal microbiota main role is to develop and improve the host immune system function via producing several bioactive compounds and preventing pathogens colonization (Brown, Kenny, & Xavier, 2019). Future studies are highly recommended to determine the routes to improve the host intestinal microbiota via balanced diet and probiotics supplements to develop the immune system function. Moreover, clinical trials have to compare if consuming the fermented foods containing the probiotics have potential antiviral activity or the activity is mainly due to the probiotic bacteria. The intake dose and duration of intake are among the factors that directly compounded for the antiviral activity of probiotics. Therefore, the correlation between the intake dose and intake period should be identified to optimize the health benefits. Nevertheless, the effects of the probiotics on the host immune cells are the indirect route for the antiviral activity. Thus, understanding these effects will explain the mechanisms of actions to prevent viral infections. Another challenge for advocating fermented foods and their probiotics is the lack of proper database to profile their microflora and bioactive compounds.

8. Conclusion

Several plant-based and animal-based fermented foods demonstrated antiviral activity towards respiratory and alimentary tracts viruses. Majority of traditional fermented foods contain probiotics bacteria and bioactive compounds that have demonstrated antiviral activities. Probiotics belonged to Lactobacilli and Bifidobacteria are among the most reported probiotics for their strong antiviral activity. Bioactive compounds in fermented foods were reported to prevent infection by targeting the virus by stimulating the host immune system. The stimulation of the immune system function involves several mechanisms such as enhancing natural killers cell toxicity, stimulating the production of pro-inflammatory cytokines, and increasing the cytotoxic of T lymphocytes ($CD3^+CD16^+CD56^+$). Although the mechanism of antiviral activity is well understood for most probiotic bacteria. However, there are very limited information on the advantage of the consumption of fermented foods that contain probiotics and bioactive compounds as majority of the studies focused on the probiotics only. Fermented foods that contain probiotics and bioactive compounds have the potential to block the viruses attachment to the cells and stimulate the immune system of the host. Future studies are recommended to focus on the profiling of the probiotics and the bioactive compounds in traditional fermented foods and determination their antiviral activity towards respiratory and alimentary tracts viruses base on dose response and duration.

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