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REVIEW ARTICLE

Bioactive metabolites in functional and fermented foods and their role as immunity booster and anti-viral innate mechanisms

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Abstract Live microorganisms in the fermented foods termed probiotics and their secondary metabolites with bioactive potential were considered as potential anti-viral capabilities through various mechanisms. Given the importance of functional and fermented foods in disease prevention, there is a need to discuss the contextualization and deep understanding of the mechanism of action of these foods, particularly considering the appearance of coronavirus (COVID-19) pandemic, which is causing health concerns and increased social services globally. The mechanism of probiotic strains or their bioactive metabolites is due to stimulation of immune response through boosting T-lymphocytes, cytokines, and cell toxicity of natural killer cells. Proper consumption of these functional and fermented foods may provide additional antiviral approaches for public benefit by modulating the immune functions in the hosts.

Keywords Anti-viral metabolites · Immunity · Fermented foods · COVID-19 · Functional foods

Introduction

The process of fermentation has long been used to increase the shelf life, flavour and functional properties of food. In addition to help food last longer, fermentation increases the nutritional value, and the probiotic bacteria present in fermented food confer health benefits that comprise reducing the risk of type 2 diabetes and cardiovascular diseases by decreasing total and LDL cholesterol (Marco et al. 2017). Multiple clinical trials investigated the advantages of fermented food and exposed the ability of kimchi and yogurt to downsize the risk of type 2 diabetes (Chen et al. 2014), Chungkookjang to decrease obesity (Byun et al. 2016),

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and the capacity of fermented milk and rye bread to control infection and irritable bowel syndrome (Laatikainen et al. 2016). Among this health promoting and infectivity demoting effects include the antiviral activity of certain fermented foods owing to the presence of live bacteria in it, and the examples are Chr. Hansen (http://www.chr-hansen.com/); Kingdom Supercultures (https://kingdomsupercultures.com/); Probitat (http://www.probitat.eu/); 3FBIO Ltd (ENOUGH) (https://www.enough-food.com/); Fermbiotics (https://www.fermbiotics.com/).

Functional foods (FFs) are distinguished by their nutraceuticals. Nutraceuticals are either whole foods or food ingredients that provide health benefits, such as disease prevention and/or treatment. This is generally associated with their microvascular, anti-inflammatory, and anti-oxidation properties in highly affected individuals. Active FFs are rich in polyphenols, terpenoids, flavonoids, and unsaturated fatty acids ingredients are among the widely active functional foods to be consumed (Alkhatib et al. 2018). Recently, Acquah et al. (2020) reported that some bioactive peptides presented many similar hormonal and neurological activities of human system (Acquah et al. 2020). On the other side, fermented food products contain probiotics (García-Burgos et al. 2020). Probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host". Covid-19 was observed to be a severe acute respiratory syndrome (SARS) which is named as SARS corona virus 2 or SARS-CoV-2 (Lai et al. 2020). Broadly, coronaviruses are large and enveloped mainly found in humans and mammals and known to cause respiratory, gastrointestinal, and neurological disease. Through genetic recombination and mutation, corona viruses can be more infectious. Stringent measures were taken by various countries based on their resource limitations, geography, population, and political factors. Although these severe interventions, since Feb. 2020 and as of March 17, 2022, the outbreak has infected almost 464 million people and killed over 6.06 million. Previous studies have shown that 65% of airborne MERS-CoV virus remains viable in the air and infectious after 60 min (Pyankov et al. 2018). The presence of SARS-CoV-2 in hospitals and entrance to department stores in Wuhan, China (Liu et al. 2020), air outlet fans in a COVID-19 outbreak center in Singapore (Ong et al. 2020) and hospital isolation rooms in Nebraska (Santarpia et al. 2020) were observed. Recently, some preliminarily results have shown that the virus can survive up to 3 h as aerosol and infect cells throughout this period (van Doremalen et al. 2020). A ferret model of SARS-CoV-2 infection that reiterates aspects of human disease has also confirmed the potential of virus airborne transmission (Kim et al. 2020). A recent study reported that SARS-CoV-2 can be viable for 4 h on copper, 24 h on cardboard, 2–3 days on plastic and stainless steel (Guo et al. 2020). Generally, SARS-CoV-2 is transmitted via respiratory pathways, but they may spread via multiple dominant routes. An acceptor individual must receive an infectious dose of the virus from a donor, either directly through the air or indirectly through deposits of the virus on various surfaces. Molecular based detection techniques, like plaque assay, Enzyme-Linked Immunosorbent Assay (ELISA), Lateral-Flow (immuno) Assay (LFA), Polymerase Chain Reaction (PCR) and Surface Plasmon Resonance (SPR) assay are identified quality and quantitative techniques for virus detection. Approximately 120 candidates are hardly working to formulate vaccines based on either nucleic acids, inactivated or live attenuated virus, and recombinant proteins (Le et al. 2020). Other approaches based on monoclonal antibodies, hyperimmune globulin will be another option. The antiviral role of FFs and fermented foods for the defence of COVID-19 is lacking and has not yet been established. However, recent reports showed that diabetes is considered a risk factor for the development and diagnosis of COVID-19 (Guo et al. 2020). Fermented foods generally contain single or multiple genera of live probiotic microorganisms that has positive impact on the host beneficially preserving the intestinal microbiota that in return has modulatory role in immune responses and human health (Fig. 1). Herein, we present antiviral role of fermented foods containing of probiotic and bioactive compounds; mechanism to stimulate immunity; case studies of viral infections and their prevention or treatment

Fig. 1 Schematic representation of applications of probiotics and bioactive metabolites

and different types of fermented foods available worldwide. This review leads to inculcating the knowledge of benefits of probiotics and fermented foods in reducing the risk of COVID-19 or other viral infections.

Antiviral activity of fermented foods containing probiotics and bioactive compounds

The plethora of fermented foods is derived from plants and animal resources. Plant-based fermented foods are tempeh, *kimchi*, *tempoyak*, and *tapai*. While animal-based fermented foods include kefir, cheese, yogurt, sauces, other dairy and meat products (Tamang et al., 2016; Raji et al. 2017; Khalil et al. 2018; Lee et al. 2020). Alcoholic beverages like fermented porridge made of sorghum and maize in South American countries (Tamang et al. 2020). Fermented foods are enriched with anti-microbial end products such as various organic acids, ethanol and peptides or bacteriocins and several studies report the antiviral potential of fermented foods *in-vitro* and *in-vivo*. The probiotic bacteria and bioactive compounds in fermented foods possess antiviral activities against gut and respiratory and viruses. These active foods stimulate immune system function by increasing the synthesis of pro-inflammatory cytokines and T lymphocytes ($CD3^+$, $CD16^+$, $CD56^+$) (Muhialdin et al. 2021). *Lactobacillus plantarum* LBP-K10 isolated from kimchi synthesised cyclic di-peptides that inhibited the growth of the influenza A (H3N2) virus (Kwak et al. 2013), while another study reported declined survival of feline calicivirus and murine norovirus proliferation during *Dongchimi* fermentation along with an increase in lactic acid bacteria (LAB) (Lee et al. 2012). Likewise, soy extracts fermented with *Aspergillus fumigatus* F-993 or *A. awamori* FB-133 showed therapeutic potential by decreasing hepatitis A virus titers *in-vitro* (Ghanem et al. 2020).

The cell free supernatant of yogurt has antiviral activity for RNA viruses such as enterovirus 71 and influenza, porcine epidemic diarrhoea virus and Coxsackie A and B viruses (Choi et al. 2010). Polyphenols, bioactive peptides, exopolysaccharides, linoleic acid, and vitamins are among the bioactive compounds found in fermented foods (Hayes and García-Vaquero 2016). Spanish sausage release angiotensin-converting enzyme inhibitor (ACE-I) when *L. pentosus* and *S. carnosus* used as a inoculum for the fermentation (Mora et al. 2015). The fermentation of *Ruditapes philippinarum* clams with *Bacillus natto* stimulate hyper-production of ACE-I peptide synthesis exerts anti-cancer property (Chen et al. 2018). However, further studies assessing the full potential of the probiotics to combat COVID-19 should be carried out (Olaimat et al. 2020) (Table 1).

Clinical impact of probiotics and bioactive compounds against viral infections in humans

High mutation rates of RNA viruses lead to their rapid evolution and better environmental adaptability (Carrasco-Hernandez et al. 2017). Various case studies report the ability of fermented and probiotic food to reduce respiratory tract infections. In one case study, some COVID-19 patients exhibited *Bifidobacterium* and *Lactobacillus* dysbiosis. The aged patients who suffered severely from COVID-19 had poor gut microbiota diversity (Dhar et al., 2020). Probiotics *L. acidophilus, Bifidobacterium*, and *Saccharomyces boulardii*, as well as minerals and vitamins, were found to reduce the complications of massive antibiotic-associated diarrhoea and *Clostridium difficile* infections. (Horowitz et al. 2020). The simultaneous intake of probiotics with azithromycin decreases the severity of *Candida albicans* infection. In another study, COVID-19-like symptoms in a young boy disappeared after 2 days of probiotic administration. (Ji et al. 2020). The administration of probiotics as an adjunct protected 97% patients against SARS-CoV2 infection. According to the recent trail, patients with severe disease recovered more easily by probiotics therapy (87.5% vs. 40.4%, $p = 0.037$) compared to non-severe ones. A human clinical trial describes oral intake of the probiotic *L. fermentum* CECT5716 increased NK cells proliferation after vaccination when compared to the group without probiotic consumption (Olivares et al. 2007). A study conducted on elderly people found to be having a significant increase in NK cell activity (Makino et al. 2010). At the same time, a randomized control clinical trial among women consumed 1073R-1-yogurt yogurt ($n = 479$) demonstrated IFN-γ production with no increase in NK cell activity (Kinoshita et al. 2019).

A control trial revealed that the probiotic strain *Lactobacillus* GG holds an adjuvant potential (Davidson et al. 2011). In children, for acute rotavirus diarrhoea, probiotic administration can relieve symptoms (Grandy et al. 2010). Multiple clinical trials are underway where the adeptness of probiotic and other dietary supplements is being investigated to alleviate the symptoms of COVID-19 infection (Table 2).

In the last two years of CoviD-19 pandemic, priority was to prevent the spreading, reduce the infections, save the lives, inculcate the knowledge of vaccination and healthy diet. Frontline health teams would benefit from the development of cutting-edge technology and the collection of available evidence. Sufficient nutrition improves health and boosts immunity, which aids in the prevention and treatment of infections. In this review we have discussed the role of probiotics in combating COVID-19 based on recent evidences, as well as their role as immune-modulators and antiviral agents. Further investigations on impact of probiotic strains and their bioactive compounds on COVID-19 affected individuals are awaiting (Kurian et al. 2021). However, more research needs to be done to study the production titres of interleukins, interferons, antibodies, and viral count due to probiotic administration during viral infection especially SARS-CoV-2.

Immune modulatory mechanisms by probiotics and fermented food

The health benefits conferred by fermented food are mainly attributed to the presence of live probiotic bacteria present which colonize the intestine and impart favourable effects. Lymphocytes, NK cells, macrophages and neutrophils are capable of mediating antibody dependent cell mediated cytotoxicity (ADCC) against virus infected cells and various probiotic and fermented food are reported to induce these immune cells. Multiple clinical trials have shown the ability of fermented food products with probiotics to improve NK cell activity and *L. casei* strain Shirota is a principal probiotic strain with this ability (Takeda and Okumura 2007). Additionally, consumption of dairy yogurt containing probiotics increased NK cell, IL-12, IFNγ and IgG1 levels in a randomized, open-label, placebo-controlled study conducted in 200 healthy volunteers (Lee et al. 2017). Probiotics play critical role in resistance against viral infections particularly in elderly people with age-related decline in lymphoid cell activity, by modulating the immune responses of hosts. Randomized control trials show that probiotic consumption significantly increased NK cell activity and CD56-positive lymphocytes in peripheral circulation in healthy elderly individuals (Gui et al. 2020). Probiotic intakes enhance cellular immunity in elderly who had poor pretreatment immune responses. Dietary supplementation of probiotic *B. lactis* HN019 increased helper (CD4 (+)) and activated (CD25 (+)) T lymphocytes, polymorphonuclear cells and natural killer cells in healthy elderly volunteers (Gill et al. 2001). Probiotic consumption found to increase natural and acquired immunity in mice and significantly improved serum antibody responses to antigens administered orally and systemically (Gill et al. 2000). Oral administration of heat killed probiotics from Mongolian dairy products augmented IFN -α, IL-12, and IFN -γ productions and increased NK cell activity leading to alleviated influenza symptoms in mice (Takeda and Okumura 2007). Similarly, oral administration of *L. rhamnoses* CRL1505 improved resistance to RSV infection in infant mice via IFN-γ and IL-10 secretion, which resulted in the activation of $CD103^+$ and $CD11b^{high}$ dendritic cells and the generation of $CD3^+CD4^+IFN\text{-}\gamma^+$ Th1 cells, with subsequent attenuation of strong Th2 reactions associated with RSV challenge (Chiba et al. 2013). An in vitro model study demonstrated the ability of probiotic bacteria to decrease vesicular stomatitis viral infection by production of nitric oxide and inflammatory cytokines such as IL-6 and IFN-γ (Ivec et al. 2007). When *L. casei* DK128 was administered into a mice intranasally, reduction in the weight and viral loads was observed, which might elicit the protection against different subtypes of influenza viruses, and mice are observed to be immune to primary infection and subsequently developed heterosubtypic secondary virus infection. The protective effect was linked to an increase in alveolar macrophage cells in the lungs and airways, the early induction of virus-specific antibodies, and lower levels of pro-inflammatory cytokines and innate immune cells (Fig. 2) (Jung et al. 2017).

Exopolysaccharides (EPS) secreted by probiotic microrganisms in fermented food contribute towards their immunomodulatory ability and antiviral potential *in-vivo*. Consumption of yogurt consisting of the starter culture *L. delbrueckii* ssp. *bulgaricus* OLL1073R-1 and secreted EPS reduced influenza virus titer in mice. The prognosis observed significant increase of anti-influenza virus antibodies such as IgA and IgG_1 along with augmented NK cell activity. In knockout mice, the presence of myeloid differentiation factor 88, EPS produced by this probiotic strain activated NK cells through IL-12- and IL-18-mediated IFN-γ production. The same probiotic strain demonstrated resistance flu virus by inducing NK cell activity in human subjects (Makino et al. 2016). EPS produced by *L. delbrueckii* TUA4408L improved the resistance to rotaviral infection by preventing the viral replication, activation of Toll-like receptor 3 rendering antiviral innate immune response in porcine intestinal epithelial cells. The study also reports *L. delbrueckii* TUA4408L and its EPS activated interferon regulatory factor (IRF)-3 and nuclear factor κB (NF-κB) signalling pathways leading to improved expression of the antiviral factors IFN-β, Myxovirus resistance gene A (MxA) and RNaseL (Kanmani et al. 2018). In addition to EPS, short chain fatty acids (SCFAs) produced by these microorganisms are observed to regulate immune responses (Parada Venegas et al. 2019). Indirectly D-phenyl lactate produced by various lactic acid bacteria regulates the immune reactions stimulated by G-protein coupled receptors by activating regulatory hydroxycarboxylic acids (Peters et al. 2019). Lactate and pyruvate also contribute to enhanced immune responses in mice models by inducing GPR31-mediated dendrite protrusion of intestinal $CX3CR1^+$ cells (Morita et al. 2019). The modulation of gut microbiota seems to be a one of the approaches to combat viral infections including COVID-19, but it needs to be further confirmed through animal models (Akour 2020). Overall, research indicates that fermented foods and probiotics contain high or low molecular weight bioactive metabolites that elicit modulations in the immune system rendering health benefits.

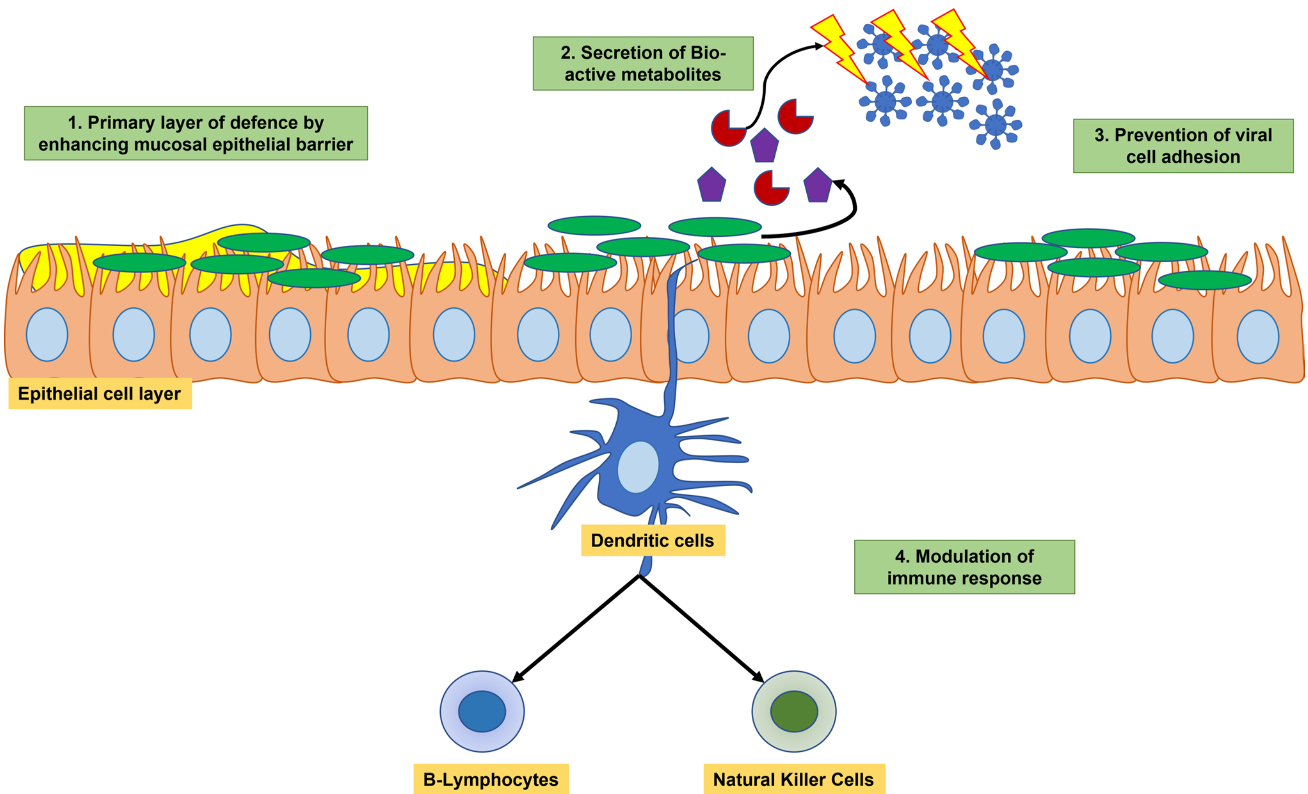

Fig. 2 Possible mechanism of anti-viral activity by probiotics

Future outlook

Fermentation by microbes applies various unconventional and uncharacterised enzymes to produce hydrolysates of protein with varying compositions of peptides. By utilizing highly efficient bacteria and by optimizing conditions of fermentation, a wide array of proteases could be produced to hydrolyse peptides and proteins with varying amino acid composition and different chain length could be synthesised in accordance to different enzyme specificity, possibly producing unique sequences of peptide with novel anti-viral bioactive properties.

It is predictable that the greatest perplexing part for researchers dealing with functional food bioactive peptides is to warrant the full bioavailability of the bioactive component after their consumption. The bioavailability of bioactive peptide is based on the capability of the peptides to resist proteolytic activity in the intestine and serum, and their potential to enter into the blood stream and consequently, exercising their biological activity. Hence, it is critical to improve the processing settings in order to retain their biological activities. Encapsulation is one of the well-characterised technologies to improve the bioavailability of functionally active peptides. This technique has been extensively applied in the nutraceutical, and food industries to encapsulate biologically active components. Encapsulation of bioactive is economically viable as this technique could avoid the interaction of the peptides with environment and/or other components in the food matrix, decrease the consequence from processing, intensify peptide stability, protect peptides against digestive enzymes and improve bioavailability.

Since functionally active foods are graded as a normal or enriched with bioactive, it has certain side effects, although the research work in this perspective is not adequate to support this statement. Even though much cell line based, and animal model studies have been widely explored to examine the bioactivity of food derived bioactive, inadequate data on human experiments is available. More research data on human clinical trials are required to validate the efficiency of food derived bioactivities. Along with this other safety parameters, like cytotoxicity, allergic response of the functional food should be evaluated before commercialization.

Viral diseases are considered as an immune compromised state resulting from poor consumption of micronutrients, vitamins and other trace elements. Several research previously indicated enhanced function of the immune system by taking those many fermented and functional foods including essential fatty and amino acids, and the above-mentioned minerals and vitamins (Calder and Kew 2002). Satisfactory diet-based consumption, and supplementation of such

Table 1 Antiviral bioactives from functional and fermented food

Probiotic microbes or Fermented foods	Salient Feature	Mode of action	References
Bifidobacterium animalis	Prevent upper respiratory tract infection	Inhibit viral replication	(Smith et al. 2013)
L. plantarum	Prevent gastroenteritis COVID virus	Reduces granulocyte, diminishes virus recovery	(Yang et al. 2017)
L. lactis	Prevent respiratory tract infection	Activates plasmacytoid dendrtitic cell	(Kokubo et al. 2019)
L. plantarum	Gastroenteritis coronaviruses (TGEV)	Reduces inflammation and tissue injury	(Yang et al. 2017)
Lactobacillus casei DN-114 001; Dan Active/Actimel	Reduced incidence and duration of RTIs	–	(Guillemard et al. 2010)
Kefir	Zika, hepatitis C, influenza, rotaviruses	Enhanced macrophage synthesis, increases phagocytosis, enhanced synthesis of (CD4+), CD8 + cells, immunoglobulins, neutrophilss, and various cytokines (IL-2, IL-12, INF-γ).	(Hamida et al. 2021)
Yoghurt	Inhibit Enterovirus	–	(Choi et al. 2010)
Fermented ginseng extracts	Inhibit influenza virus H1N1, H3N2, H5N1, and H7N9 strains	Viral inoculation with extract of ginseng formed better immune responses against the 2^0 infection with homologous and heterosubtypic virus.	(Wang et al. 2018)
Black ginseng	Inhibit influenza virus	Black ginseng improved the levels of GM-CSF and IL-10 at the time of infection	(Kim et al. 2019)
Dietary xylitol	Inhibit influenza virus A	–	(Yin et al. 2014)
Chongkukjang (Traditional Korean feremented food)	Influenza virus A	–	(Wei et al. 2015b)
Resveratrol (From red grapes)	Inhibit Epstein-Barr virus	Downregulation of antiapoptotic proteins	(De Leo et al. 2012)
Zingiberofficinale (Ginger)	Anti-chikungunya activity	–	(Kaushik et al. 2020)
Curcumin	Inhibit Zika and chikungunya viruses	Curcumin interferes with virus-cell binding.	(Mounce et al. 2017)

Table 2 Ongoing clinical trials where probiotics and dietary supplements are used against COVID-19

No.	Clinical trial identifier	Intervention	Aim
1	NCT04621071	Probiotics	Evaluation of the efficacy of probiotics to dcrease the duration and symptoms of COVID-19
2	NCT04458519	Probiorinse	Reduction of severity of COVID-19 symptoms
3	NCT04390477	Probiotic	Effect of probiotic on COVID-19 infection
4	NCT04366180	*L. coryniformis* K8	Effect of probiotic in the incidence and prevention of COVID-19 infection in health workers
5	NCT04734886	*L. reuteri* DSM 17,938	Impact of probiotic supplementation on SARS-CoV-2 specific antibody response following COVID-19 infection
6	NCT04666116	Dietary supplements including probiotics	To check the changes in viral load in COVID-19 infection
7	NCT04847349	Probiotics	Efficacy of probiotic intervention to boost the immunity in unvaccinated people infected previously with SARS-CoV-2
8	NCT04420676	Synbiotic (Omnibiotic AAD)	To check the ability to reduce gastrointestinal problems in COVID-19 patients
9	NCT04813718	Omni-Biotic Pro Vi 5	Analysis of post-Covid syndrome
10	NCT04399252	*L. rhamnosus* GG	In order to study the consequence of microbiome in COVID-19 exposed household contacts

functional foods, contribute to sustaining optimal levels in the humans, which improves several characteristics of the immune function, and provides an important antiviral prevention of COVID-19. On the other hand, less strong immune activation has been proved to be the primary threat factor for COVID-19, which makes it appropriate to define the defensive role of functional food particles benefits in the perspective of preventing COVID-19 and other viral diseases (Grant et al. 2020).

Examination of outcome of viral disease management in high-risk populations and aged people is very central. Large number of viral and COVID 19 infection rate is reported in older adults and persons with other co-morbidities. The prevalence of COVID-19 in people with diabetes is high and now considered a hazard factor for the progression COVID-19 (McGurnaghan et al. 2021). Therefore, best "immune-modulating" functional foods could provide the finest prevention and progression of the viral diseases. The use of functional foods to combat viral diseases would especially benefit the elderly, which has become a growing sector of the world population.

Conclusion

Fermentation by microbe's functions as a potent technique to supplement foods with biologically active peptides from various animal or plant sources. These bioactive compounds produced in the fermented foods tends to boost the immune response either directly or indirectly against the viral infections by modulating the lymphocytes, NK cells, macrophages and neutrophils that are capable of mediating antibody dependent cell mediated cytotoxicity. Several works have been documented to unveil novel bioactive components from fermented foods and other edible plant by products. It is possible that the varieties of biopeptides from various fermented food will continue to develop in the coming years. Further awareness of these health beneficial fermented foods and their compositions could help in improving the health and wellness of the society.

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Declarations

The authors declare that the work described has not been published before (except in the form of an abstract, a published lecture or academic thesis), it is not under consideration for publication elsewhere, its submission to JFST publication has been approved by all authors as well as the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder, and JFST will not be held legally responsible should there be any claims for compensation or dispute on authorship.

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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