



Review

Traditional fermented foods with anti-aging effect: A concentric review

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ABSTRACT

Fermentation has been applied since antiquity as a way to preserve foodstuff or as a necessary step in the production of a variety of products. The research was initially focused on accurate description of production procedure and identification of parameters that may affect the composition and dynamics of the developing micro-communities, since the major aim was standardization and commercial exploitation of the products. Soon it was realized that consumption of these products was associated with an array of health benefits, such as anti-hypertensive, anti-inflammatory, anti-diabetic, anti-carcinogenic and anti-allergenic activities. These were credited to the microorganisms present in the fermented products as well as their metabolic activities and the bio-transformations that took place during the fermentation process. Aging has been defined as a gradual decline in the physiological function and concomitantly homeostasis, which is experienced by all living beings over time, leading inevitably to age-associated injuries, diseases, and finally death. Research has focused on effective strategies to delay this process and thus increase both lifespan and well-being. Fermented food products seem to be a promising alternative due to the immunomodulatory effect of microorganisms and elevated amounts of bioactive compounds. Indeed, a series of anti-aging related benefits have been reported, some of which have been attributed to specific compounds such as genistein and daidzein in soybeans, while others are yet to be discovered. The present article aims to collect and critically discuss all available literature regarding the anti-aging properties of fermented food products.

1. Introduction

Among the factors affecting the intestinal microbiota, nutrition seems the most easily regulated one. The intestinal microbiota is affected by the type and functionality of the dietary components as well as the nutrition model (Western-style nutrition, Mediterranean diet, vegetarian nutrition, etc.) (Kabak & Dobson, 2011). Fermentation is one of the most economical food processing and storage methods that has been applied for centuries. It is a traditional technology that uses the growth and metabolic activities of several beneficial microorganisms for the preservation and bioconversion of food materials (Terefe, 2016). This process also enhances the microbial stability and safety of the final product, increases the shelf life of perishable raw materials, improves mineral bioavailability, digestibility of proteins and carbohydrates, and

also the organoleptic features of the product (Nout, 2013; Tamang, Shin, Jung, & Chae, 2016; Terefe, 2016). Besides, associations between consumption of certain fermented foods with specific health benefits have been established. The inverse association between the consumption of fermented dairy products with the risk of type 2 diabetes, cardiovascular diseases and all-cause mortality (Goldbohm, Chorus, Galindo Garre, Schouten, & van den Brandt, 2011; Sluijs et al., 2012; Sonestedt et al., 2011), as well as the anti-diabetic, anti-obesity and anti-aging effect of fermented kimchi (An et al., 2013; Cui et al., 2015; Kim, Park, Kim, Ahn, & Cho, 2011a), may serve as examples.

Health-promoting actions of fermented foods have been attributed to the metabolic activities of the microbiota that develops during fermentation. Very often, the isolation of microbial strains with very interesting health-promoting properties is reported. For example,

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Lactobacillus helveticus strain R389 that was isolated from Swiss cheese was reported to contribute to the immune-enhancing and antitumor activities of fermented milk through the release of bioactive compounds (de LeBlanc & Perdígón, 2010). *Lb. plantarum* strain pl27 was isolated from kefir grains and was reported to lower serum total and low-density lipoprotein cholesterol and triglycerides concentration when fed to hypercholesterolemic Sprague-Dawley rats (Huang et al., 2013). *Enterococcus faecium* strain A86, *Lb. plantarum* strains T211, H10, H5, L3 and *Leuconostoc gelidum* strain A16 that were isolated from pizza dough and sourdough increased iron, manganese, and zinc solubility during wheat dough fermentation through their phytate-degrading capacity (Anastasio et al., 2010).

Recently, there is a reintroduced interest in the study of various traditional fermented food products, primarily driven by their claimed health beneficial effects both as a source of probiotic organisms and health-promoting compounds. The anti-aging potential of fermented foods has been given much consideration over the last decade and promising results have been obtained. The present review aims to collect and critically discuss all available literature regarding the anti-aging properties of fermented food products.

2. Types of fermented foods around the world with potential health beneficial effect

2.1. Health benefits of fermented foods

Fermented foods (FFs) have been in use from the beginning of civilization. The nature of FF varies according to the geographical region, which helps to describe the lifestyle of a domestic population. FFs can be broadly divided into three groups: 1. Dairy-based FFs (e.g. Kefir), 2. Meat-based FFs (e.g. Sausages, and Salami), and 3. Fruit and Vegetable-based FFs (e.g. Kimchi). The types and use of FF differ among the people around the world. The composition, preparation procedures, chemical, and biological constituents, as well as the health benefits of several Asian FFs, have been reported in recent studies (Patra, Das, Paramithiotis, & Shin, 2016; Sivamaruthi, Kesika, & Chaiyasut, 2018a, 2018b; Surono, 2015; Swain, Anandharaj, Ray, & Parveen Rani, 2014). The health benefits of various fermented foods are presented in Table 1.

Most of the African FFs are enriched with bioactive LAB strains (Franz et al., 2014). LAB strains isolated from African FFs have been reported for anti-shigellosis (Opere, Aboaba, & Ugoji, 2003) and anti-diarrheal activity (Anukam, Osazuwa, Osadolor, Bruce, & Reid, 2008; Lei, Friis, & Michaelsen, 2006), gastrointestinal tract health regulation, enhancement of human immune system and antiretroviral treatment responsiveness (Hummelen et al., 2011a, 2011b; Reid, 2010; Whaling et al., 2012).

The commonly used LAB-mediated FFs of Africa play a major role in the improvement of the general health status of Africans. Especially, diarrhea is a common health issue in most of the African countries due to unhygienic life practices, which is closely associated with the economic status of the country. The introduction and use of LAB-mediated FFs significantly reduced the incidence of bacterial infection and diarrheal outbreaks in Africa (Oyewole, 1997).

Kim et al. (2016a) reviewed the influence of FFs on the brain and cognitive functions. The authors detailed all the reports on the effect of FFs supplementation on cognitive functions (memory, anxiety, etc.) and brain activity. Fermented dairy products (Camembert cheese extracts, fermented milk, and fermented soy milk), cereal fermented products (Tempeh, fermented soybean products, Cheonggukjang, rice vinegars, and red mold rice), fermented fruits (fermented papaya, and grape), fermented vegetables (Kimchi), fermented roots (fermented garlic, and fermented ginseng), and fermented tea were acknowledged for their involvement in the improvement of cognitive and brain function. The changes in phytochemical content during the fermentation process, hypothalamic pituitary adrenal axis inhibition and regulation of neurotransmitters were considered as the mechanisms behind the health

benefits of FFs (Kim et al., 2016a).

The fermentation process alters the phytochemical composition of raw materials (Li, Chang, Guo, Wang, & Guo, 2019). The decarboxylation of L-glutamate produces gamma-aminobutyric acid (GABA), which was mediated by the bacterial glutamate decarboxylase (GAD) enzyme. GABA, is produced by microorganisms, plants, and mammals and is commonly distributed in numerous foods. It acts as a significant inhibitory neurotransmitter in the mammalian nervous system, and it plays a vital role in the regulation of the blood pressure and many other physiological functions in the body (Diana, Quilez, & Rafecas, 2014; Gan, Li, Gunaratne, Sui, & Corke, 2017; Jannoey et al., 2010). In this context, there is a need for enhancing the amount of GABA content in foods, by the application of several food processing methodologies, including fermentation (Dhakal, Bajpai, & Baek, 2012). It has been reported that edible seeds such as chickpea, kidney bean, soybean, adzuki bean, faba bean, lentil, buckwheat, wheat, quinoa, rice, amaranth, spelt, millet, oat, rye, and their products are a natural source of GABA and application of lactic acid fermentation can increase its content several folds (Fig. 1) (Gan et al., 2017). Indeed, this was verified by recent studies, conducted either by using lactic acid bacteria strains with high GABA-producing capacity of by spontaneous fermentation for the production of fermented dairy products (Chen, Alcazar, Yang, Lu, & Lu, 2018; El-Fattah, Sakr, El-Dieb, & Elkashef, 2018; Han, Liao, Wu, Gong, & Bai, 2020; Tofalo et al., 2019; Yu et al., 2020), sourdough bread (Kim, Kim, Chung, & Han, 2019; Venturi, Galli, Pini, Guerrini, & Granchi, 2019), fermented seeds (Ding et al., 2020; Kawee-ai & Seesuriyachan, 2019), fermented vegetables (Lee, Shim, Yao, Kim, & Kim, 2018; Park, Garcia, Youn, Park, & Lee, 2019; Tanamool, Hongsachart, & Soemphol, 2020), fermented soybean products (Bao, Huang, Liu, Han, & Chen, 2020; Hwang et al., 2018), beverages (Choe, Lim, & Lee, 2019; Woraharn et al., 2016; Zhang et al., 2020), fish sauce (Taoka et al., 2019), as well as various types of tee (Horie et al., 2019; Tong, Liu, Kang, Zhang, & Kang, 2019; Yilmaz, Ozdemir, & Gokmen, 2020).

Kefir is a unique fermented milk product, made with kefir grains and milk, commonly cow's milk. Kefir grains contain a mixture of potentially probiotic strains (LAB, yeasts, acetic acid bacteria, *Bacillus* spp, and filamentous fungi). The nutritional composition of kefir varies based on the kefir grains, types of milk used as well as fermentation and storage conditions. Several studies highlighted the health benefits (antibacterial, hypocholesterolemic, antihypertensive, anti-inflammatory, anti-diabetic, antioxidant, anti-carcinogenic and anti-allergenic activities) of kefir. The preparation methods, composition, microbial community, and health impact of kefir consumption have been detailed in recent studies (Nielsen, Gürakan, & Ünlü, 2014; Rosa et al., 2017). Similarly, kimchi has been reported to possess antiaging, antiobesity, anticancer and anti-constipation properties (Kim et al., 2011a, 2011b; Terefe, 2016).

2.2. In vitro studies

Lb. plantarum strain isolated from Ogi, which is a traditionally fermented African food, exhibited several bioactive properties such as antimicrobial (active against both Gram-positive and Gram-negative bacteria), hepatoprotective (significantly reduced the liver damage markers), anticholesterolemic and immunostimulatory activities (Oyetayo & Isah, 2006).

Monascus-fermented red mold rice (RMR) has been studied for anticancer activity using the human breast cancer cell line (MCF-7 cells). The results suggested that the traditional fermented red mold rice was cytotoxic and induced the apoptosis in cancer cells. RMR can be used as an alternative and complementary functional food to prevent the incidence of breast cancer (Lee, Lee, Hwang, Lee, & Wang, 2013).

The indole alkaloid derivatives of Kanjang (traditional Korean fermented soy sauce) exhibited *in vitro* neuroprotective (anti-neuroinflammatory) activity via reducing the release of the inducible nitric acid

Table 1
Health benefits of fermented foods.

Fermented foods	Origin/study conducted region	Study type	Dose and Duration	Active compounds	Health claims	Reference
Asian Fermented foods						
Fermented milk	Japan	RPCT	200 ml of FM/day for 6 weeks	Probiotics (<i>Lb. acidophilus</i> L-92)	Anti-allergic activity	(Shida et al., 2005)
Fermented milk	China	RPCT	100 g of FM for 2 weeks	Probiotics (<i>B. lactis</i> DN-173010)	Anti-constipation activity in adults	(Yang et al., 2008)
Fermented milk	Japan	Open case-controlled study	4×10^{10} cells per day for 3 months	Probiotics (<i>Lb. casei</i> strain Shirota)	Improved health condition of people affected by gastroenteritis.	(Nagata et al., 2011)
Fermented milk	Japan	RPCT	1.0×10^{11} cells per day for 12 weeks	Probiotics (<i>Lb. casei</i> strain Shirota)	Reduced upper respiratory tract infections	(Shida et al., 2017)
Fermented milk	Japan	RPCT	200 g of FM (10^6 or 10^7 cell/g) per day for 12 weeks	Probiotics (<i>Lb. gasseri</i> SBT2055)	Reduced the abdominal adiposity.	(Kadooka et al., 2010; 2013)
Fermented milk product (Kefir)	The Caucasus, Tibetan mountains	–	–	Mixture of probiotics	Antibacterial, hypocholesterolemic, antihypertensive, anti-inflammatory, anti-diabetic, antioxidant, anti-carcinogenic, anti-allergenic activities.	(Rosa et al., 2017)
Fermented milk product (Kefir)	Japan	<i>In vivo</i> (mice model)	0.2 ml per day for 12 weeks	Mixture of probiotics	Anti-obesity, and anti-non-alcoholic fatty liver disease activity	(Kim et al., 2017)
Fermented milk product	Japan	RPCT	190 g per day for 8 weeks	Probiotics (<i>Lb. helveticus</i>), and lactononadecapeptide	Improved the cognitive function of healthy adults	(Ohsawa et al., 2018)
Fermented Soybean Paste (Miso)	Japan	RPCT	6 weeks	Soy phytochemicals	Anti- hypertension	(Nakamura, Aoki, Yamada, & Kubo, 2003)
Fermented soy sauce (Ganjang)	Korea	<i>In vivo</i> (rat model)	10 ml/kg per day for 9 weeks	Soy phytochemicals and bioactive microbes	Anti- hypertension	(Mun et al., 2017)
Fermented soybean paste (Doenjang)	Korea	RPCT	9.9 g per day for 12 weeks	Soy phytochemicals and bioactive microbes	Anti-obesity, visceral fat reduction	(Lee et al., 2012b)
Fermented soy sauce (Kanjang)	Korea	<i>In vitro</i> (lipopolysaccharide-induced BV2 microglial cells)	–	Indole alkaloid derivatives	Anti-neuroinflammatory activities	(Kim et al., 2016b)
Fermented ginseng	Korea	<i>In vivo</i> (mice model)	0.25% FG + 2.5×10^8 CFU/ml of PM (or) 0.50% FG + 5×10^8 CFU/ml of PM (or) 1.0% FG + 1×10^9 CFU/ml of PM	Ginseng and probiotics (<i>B. longum</i> BORI and <i>Lb. paracasei</i> CH88)	Anti-obesity effect	(Kang et al., 2018)
Fermented dairy, vegetable, cereal, and legume products	Korea, Indonesia, Japan, China	–	–	Phytochemicals, and probiotics	Improved the brain and cognitive function	(Kim et al., 2016a)
Fermented soybean (Douchi)	China	<i>In vitro</i>	–	Soy phytochemicals	Antioxidant activity	(Wang et al., 2007)
Red mold rice	Asia	<i>In vitro</i> (Human breast adenocarcinoma cells)	–	Polyketides	Antidiabetic, antifatigue, anti-inflammatory, antihypertensive, antihyperlipidemic, antioxidant, anticancer, and anti-Alzheimer's activity	(Lee et al., 2013)
African fermented foods						
Lactic acid bacteria fermented foods	Africa	–	–	Probiotics Lactic acid bacteria	Anti-diarrhea, and anti-infection	(Oyewole, 1997)
Fermented corn product (Ogi)	Africa	–	–	<i>Lb. plantarum</i>	Antimicrobial, Hepatoprotective, Anticholesterolenic, Immunostimulatory activities	(Oyetayo & Isah, 2006)
A mixture of fermented popcorn flour, Bambara groundnut flour, African locust bean flour	Nigeria	–	–	–	Improved the general health status	(Jiarotimi & Keshinro, 2012; Magrone et al., 2008)

RPCT: Randomized placebo-controlled trial.

Edible seeds and their products	Inoculated microbes	GABA content		Unit	References
		Nonfermented samples	Fermented samples		
Chickpea (<i>Cicer arietinum</i>)	<i>Lb. plantarum</i> C48	18.0	615	mg/kg DW	(Coda and others 2010)
	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	18.0	1031	mg/kg DW	
Faba bean (<i>Vicia faba</i> L.)	<i>Lb. plantarum</i> VTT E-133328	~50.0	~1000	mg/kg DW	(Coda and others 2015)
Kidney bean (<i>Phaseolus vulgaris</i>)	<i>B. subtilis</i> CECT 39 ^T (ATCC 6051)	3.20	2.61 to 2.69	mg/g DW	(Limon and others 2015)
	<i>Lb. plantarum</i> CECT 748 ^T (ATCC 14917)	2.27	6.76 to 9.90	mg/g DW	
Lentil (<i>Lens culinaris</i>)	Natural fermentation	2.27	7.54 to 10.6	mg/g DW	
	<i>Lb. plantarum</i> CECT 748 ^T (ATCC 14917)	~4.40	~6.00 to 7.16	mg/g DW	(Torino and others 2013)
	Natural fermentation	~4.40	~7.50 to 10.4	mg/g DW	
	<i>B. subtilis</i> CECT 39 ^T (ATCC 6051)	~3.20	~4.00 to 6.54	mg/g DW	
Soybean (<i>Glycine max</i>)	<i>Lb. plantarum</i> C48	24.0	57.0	mg/kg DW	(Coda and others 2010)
	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	24.0	39.0	mg/kg DW	
	<i>A. oryzae</i> FMB 546471 and <i>L. brevis</i> GABA100	~0.15	~3.60 to 6.60	g/kg DW	(Kim and Ji 2014)
Amaranth (<i>Amaranthus hypocondriacus</i>)	<i>Lb. plantarum</i> C48	12.0	654	mg/kg DW	(Coda and others 2010)
Buckwheat (<i>Fagopyrum esculentum</i>)	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	12.0	816	mg/kg DW	
	<i>Lb. plantarum</i> C48	40.0	643	mg/kg DW	
Millet (<i>Panicum miliaceum</i>)	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	40.0	562	mg/kg DW	
	<i>Lb. plantarum</i> C48	15.0	110	mg/kg DW	
	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	15.0	231	mg/kg DW	
Oat (<i>Avena sativa</i>)	<i>Lb. plantarum</i> C48	27.0	185	mg/kg DW	
	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	27.0	206	mg/kg DW	
	<i>A. oryzae</i> var. <i>effuses</i> 3.2825	57.1	59.0 to 331	μg/g DW	(Cai and others 2014)
	<i>A. oryzae</i> 3.5232	57.1	59.0 to 435	μg/g DW	
	<i>R. oryzae</i> 3.275	57.1	59.0 to 126	μg/g DW	
Quinoa (<i>Chenopodium quinoa</i>)	<i>Lb. plantarum</i> C48	78.0	415	mg/kg DW	(Coda and others 2010)
	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	78.0	176	mg/kg DW	
Rice (<i>Oryza sativa</i>)	<i>Lb. plantarum</i> C48	12.0	24.0	mg/kg DW	
	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	12.0	30.0	mg/kg DW	
	<i>M. purpureus</i> CMU 001	N.M.	1.24 to 28.4	mg/g DW	(Jannoe and others 2010)
	<i>Lc. lactis</i> RO50	N.M.	120 to 150	mg/100 g DW	(Saikusa and others 2016)
Rye (<i>Secale cereale</i>)	Several LAB	N.M.	11.7 to 168	mg/kg DW	(Rizzello and others 2008)
	<i>Lb. plantarum</i> C48	12.0	39.0	mg/kg DW	(Coda and others 2010)
	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	12.0	75.0	mg/kg DW	
Spelt (<i>Triticum spelta</i>)	<i>Lb. plantarum</i> C48	3.00	72.0	mg/kg DW	
	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	3.00	259	mg/kg DW	
White wheat (<i>Triticum aestivum</i> Appulo cv)	Several LAB	N.M.	12.7 to 101	mg/kg DW	(Rizzello and others 2008a)
Common wheat (<i>Triticum aestivum</i>)	<i>Lb. plantarum</i> C48	7.00	63.0	mg/kg DW	(Coda and others 2010)
	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	7.00	70.0	mg/kg DW	
Durum wheat (<i>Triticum durum</i>)	<i>Lb. plantarum</i> C48	19.0	75.0	mg/kg DW	
	<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	19.0	84.0	mg/kg DW	
Adzuki bean milk	<i>Lc. lactis</i> subsp. <i>lactis</i> and <i>L. rhamnosus</i> GG	~28.0	~68.0	mg/100 mL	(Liao and others 2013)
Black bean milk	<i>Lb. brevis</i> FPA 3709	1.07	1.34 to 4.04	mg/mL	(Ko and others 2013)
Chickpea milk	<i>Lb. plantarum</i> M-6	~140	~150 to 537	mg/L	(Li and others 2016)
Soy milk	A mixture of LAB	~100	~130 to 180	mg/g DW	(Tsai and others 2006)
	<i>Lb. casei</i> Zhang	~24.5	~43.0	mg/L	(Li and others 2012)
	<i>Bb. animalis</i> V9 (CP001892)	~24.5	~45.6	mg/L	
	<i>Lb. acidophilus</i> NCFM	~24.5	~36.0	mg/L	
	<i>Lb. rhamnosus</i> GG	~24.5	~39.0	mg/L	
	<i>Bb. animalis</i> BB12	~24.5	~39.5	mg/L	
	<i>Lb. casei</i> Shirota	~24.5	~45.0	mg/L	
Soybean paste	Natural fermentation	~5.00	~5.00 to 80.0	μmol/g DW	(Jung and others 2016)
Oat flakes beverage	<i>Lb. plantarum</i> LP09	~4.00	~5.00	mg/kg	(Nionelli and others 2014)
Rice-based sunsik	A mixture of microorganisms	26.0	66.0	mg/100 g DW	(Koh and others 2014)
Wheat-based dosa	<i>Lb. plantarum</i> MNZ	~0.00	~0.00 to 115	mg/kg	(Zareian and others 2015)
Wholemeal wheat	Several LAB	N.M.	11.0 to 259	mg/kg DW	(Rizzello and others 2008)

A., *Aspergillus*; B., *Bacillus*; Bb, *Bifidobacterium*; Lb, *Lactobacillus*; R., *Rhizopus*; N.D., not detected. DW, dry weight.

Fig. 1. An example of the potential effect of fermentation process on the elevation of GABA content in various edible seeds and their products. Reproduced with permission from Gan et al. (2017) (originally Table 2).

level in BV2 cells, and the further investigation revealed that the anti-inflammatory activity of Kanjang derived compounds are related to the inhibition of nuclear factor- κ B pathway (Kim et al., 2016b).

2.3. In vivo studies using an animal model

Diet supplementation with Ganjang, a traditional Korean fermented soy sauce, significantly reduced the blood pressure, serum renin and aldosterone levels as well as mRNA levels of Na^+ transporter, NKAa1, NHE3, NBC, and CAII in Sprague-Dawley rats. The volume of urine was found to be increased during Ganjang supplementation. The results proposed that the consumption of Ganjang has anti-hypertension effects even though it contains more salts (Mun, Sohn, Kim, & Cha, 2017).

Kefir supplementation exhibited a significant reduction in body mass, liver lesion scores and pro-inflammatory markers while increasing the lactic acid bacterial load in high-fat-diet-induced obese mice. The genes associated with fatty acid (FA) oxidation, PPAR α and AOX were significantly up-regulated in the kefir fed mice. The study

stated that the consumption of kefir showed anti-obesity and anti-non-alcoholic fatty liver activity by positive regulation of the gut microbiota and FA oxidation (Kim et al., 2017).

The fermented ginseng, *B. longum* BORI, and *Lb. paracasei* CH88 was supplemented to high fat diet-fed mice for nine weeks. The supplementation reduced the adipocyte size and suppressed weight gain. The positive improvements were observed in fasting blood glucose level, excretory cholesterol level in feces, and expression of TNF- α in adipose tissue. The results proved that the mixture of probiotics and fermented ginseng intervention exhibited anti-obesity activity in high fat diet-fed mice (Kang, Li, & Ji, 2018).

2.4. Clinical trials

Yang et al. (2008) investigated the effect of fermented milk on randomly allocated Chinese women with constipation. Women (67 individuals) in the test group consumed the fermented milk, which contained the probiotic strain *Bifidobacterium lactis* DN-173010

(1.25×10^{10} CFU per day) and yogurt starters (*Streptococcus thermophilus*, *Lb. delbrueckii* subsp. *bulgaricus*; 1.2×10^9 CFU per day). Women (68 individuals) in the control group consumed acidified milk not containing live bacteria. After the first and second week of supplementation of fermented milk, the defecation condition scores, stool consistency, and frequency were found to be improved in adults suffered from constipation (Yang et al., 2008).

A single-blind, randomized placebo-controlled trial was conducted by Ishida et al. (2005), during the Japanese cedar pollination seasons of the year 2002 and 2003 and studied the effect of *Lb. acidophilus* L-92 mediated fermented milk on the Japanese people with symptoms of cedar pollen allergy. A total of 23 in-house volunteers who were allergic to cedar pollen participated in the 2002 study and the test group (12 individuals) consumed fermented milk containing 5×10^{10} CFU of L-92 twice daily for 6 weeks. A total of 20 in-house volunteers allergic to cedar pollen participated in the 2003 study and the test group (10 individuals) consumed fermented milk containing 2×10^{10} CFU of L-92 daily for 10 weeks. During both 2002 and 2003 study, the volunteers of the placebo group daily consumed an appropriate amount of sterilized pre-fermented mixture prepared with acidity (adjusted using lactic acid) similar to that of the fermented milk. Consumption of fermented milk improved the ocular symptom-medication score (2002 study) and distress of life score (2003 study) among the Japanese people, who suffer from cedar-pollen allergy (Ishida et al., 2005).

An open case-controlled study was performed to investigate the effect of fermented milk containing *Lb. casei* strain Shirota (YIT 9029) on fever caused due to the outbreak of norovirus gastroenteritis during the winter season (December month of the year 2006) in Yuyu municipal health service facility (residential homes for long-term care) for elderly people (Nagata et al., 2011). After 2 weeks of restricted (avoiding LAB containing product) period, the elderly people (39 individuals) of the test group consumed fermented milk containing 4×10^{10} cells of YIT 9029 for 3 months (October to December 2006). Fermented milk was not provided to elderly people (38 individuals) of the control group. Daily consumption of fermented milk significantly reduced the duration of the fever caused by norovirus gastroenteritis. Nagata et al. (2011) also conducted a controlled study to investigate the effect of fermented milk on the fecal microflora of the long-term residents of the same health care facility. Ten elderly people consumed the fermented milk containing 4×10^{10} cells of YIT 9029 after two weeks of the restricted period. The fecal sample was collected before starting the ingestion of fermented milk and during the period (at first and second month) of consumption of fermented milk. The intake of fermented milk increased the load of beneficial microbes and reduced the *Enterobacteriaceae* family members in elderly people. The study suggested that the daily consumption of fermented milk improved the imbalanced microflora, but the consumption of fermented milk containing probiotic did not protect the elderly from disease (Nagata et al., 2011).

A randomized controlled trial was conducted by Shida et al. (2017), during the winter season to study the effect of fermented milk containing YIT 9029 on healthy middle-aged male individuals (office workers) with upper respiratory tract infections. Individuals (forty-seven) of the control group consumed unfermented milk and individuals (forty-nine) of the test group consumed fermented milk containing 1×10^{11} CFU of YIT 9029 daily for 12 weeks. The samples (blood and saliva) were collected at 0, 6th, and 12th weeks of the intervention period. The intervention (12 weeks) of fermented milk significantly reduced the incidence and duration of upper respiratory tract infections among the healthy middle-aged working people. Shida et al. (2017) reported the positive effect of fermented milk on upper respiratory tract infections with strong evidence.

A randomized, double-blind, controlled trial was conducted by Ohsawa, Nakamura, Uchida, Mizuno, Yokogoshi (2018), to investigate the effect of fermented milk containing *Lb. helveticus* CM4 and lactonadaceptide on the cognitive function in healthy middle-aged

Japanese adults with forgetfulness. A total of sixty-one individuals participated in the study and the individuals of the test group consumed one bottle of *Lb. helveticus*-fermented milk (190 g per day) containing lactonadaceptide (2.4 mg per bottle) daily for eight weeks. The placebo drink contained no CM4 and lactonadaceptide. The supplementation of *Lb. helveticus*-fermented milk containing lactonadaceptide significantly improved the cognitive functions, especially attention and delayed memory in healthy middle-aged Japanese adults (Ohsawa, Nakamura, Uchida, Mizuno, & Yokogoshi, 2018).

Randomized, double-blind, controlled trials were conducted by Kadooka et al. (2010; 2013) to study the effect of fermented milk containing *Lb. gasseri* SBT2055 on abdominal adiposity in healthy Japanese adults with the large visceral fat area. Fermentation was carried out by the yogurt starters (*Str. thermophilus*, *Lb. delbrueckii* subsp. *bulgaricus*); a viable population of the probiotic strain *Lb. gasseri* SBT2055 was added to the fermented milk. In the 2010 study, test group (forty-three participants) consumed fermented milk (100 g twice daily) containing SBT2055 (10^8 CFU per gram), and control group (forty-four participants) consumed fermented milk (100 g twice daily) containing no SBT2055 cells for 12 weeks (Kadooka et al., 2010). In the 2013 study, sixty-nine individuals of one test group consumed fermented milk (100 g twice daily) containing SBT2055 (10^6 CFU per gram), and seventy-one individuals of another test group consumed fermented milk (100 g twice daily) containing SBT2055 (10^7 CFU per gram) for 12 weeks. Seventy individuals of the control group consumed fermented milk (100 g twice daily) containing no SBT2055 cells for 12 weeks (Kadooka et al., 2013). The body composition and anthropometric measurements were noted at weeks 0, 4, 8, and 12 of consumption and at the 4th week after the end of consumption period. The abdominal fat areas were measured at weeks 0 and 12, in the 2010 study and at weeks 8 and 12 in the 2013 study. The supplementation of fermented milk containing SBT2055 (10^8 CFU per gram) significantly reduced abdominal adiposity (Kadooka et al., 2010). The consumption of fermented milk containing a low dose of SBT2055 (10^{6-7} CFU per gram) also exhibited abdominal adiposity reducing activity but the positive effect might require constant consumption of fermented milk containing SBT2055 (Kadooka et al., 2013). Both studies showed strong evidence of the positive effect of fermented milk consumption.

A randomized, double-blind, controlled trial was conducted by Lee, Chae, Cha, and Park (2012b) to investigate the effect of doenjang (Korean fermented soy paste) in overweight individuals and correlate it with a polymorphism upstream of uncoupling protein-1 (UCP-1) gene. The test group (19 individuals with A allele; 31 individuals with G allele) consumed three tablets (9.9 g; a total weight of 3 tablets) containing freeze-dried doenjang (9.8 g obtained from 40 g of doenjang) and the control group (21 individuals with A allele; 31 individuals with G allele) consumed three tablets (same weight as test tablets) containing freeze-dried placebo (9.8 g obtained from 16.5 g of placebo) daily for 12 weeks. The placebo (16.5 g) consisted of chrysanthemum tea powder (0.3 g), cocoa powder (0.1 g), cowpea powder (1.3 g), meju (0.1 g), oil powder (4.7 g), rice powder (2.8 g), salt (3.5 g), soy sauce (2.9 g), and wheat flour (0.8 g). Doenjang (40 g) consisted of meju (20 g), salt (3.8 g), and water (16.2 g). The supplementation with Doenjang significantly decreased the visceral fat and increased the free FA content in subjects with G allele of UCP-1 polymorphism while no notable changes were found in subjects with wild-type alleles. The study stated that Doenjang supplementation activated the lipolysis that may induce the deliverance of free FAs in subjects with G allele of UCP-1 polymorphism. However, more detailed studies are required to elucidate the molecular mechanisms responsible for the association between UCP-1 allelic status, Doenjang intervention and visceral fat reduction (Lee et al., 2012b).

3. Anti-aging properties of fermented foods

Aging is an unavoidable, universal, multifactorial and complex

Table 2
Anti-aging related properties of fermented foods.

Fermented food	Experimental models	Biological Activities	References
Red wine polyphenols	Lymphomonocytes Human B cells	Promoted the expression of IL-12, IL-6, IL-1 β , IL-10, IgA, and IgG.	(Magrone et al., 2008)
Rice wine	Human fibroblasts Human keratinocytes	Promoted the type I procollagen. Reduced the UV-induced MMP-1 and TNF- α . Increased antioxidant activity, and laminin-5 expression.	(Seo et al., 2009)
Nuruk extracts	Human hepatoma, HepG2	Free radical scavenging activity. Increased expression of SOD in H ₂ O ₂ -treated HepG2 cells.	(Lee et al., 2012c)
Fermented soybean (Natto)	<i>Caenorhabditis elegans</i>	Life span extension. Delayed the lipofuscin accumulation.	(Ibe et al., 2013)
Fermented gastrodia extracts	–	Antioxidant activity	(Choi et al., 2013)
Fermented <i>Lespedeza cuneata</i> G. Don extract	Human fibroblasts	Inhibited the elastase, and UV-induced MMP-1 expressions. Increased the type I procollagen synthesis.	(Seong et al., 2017)
Fermented milk	–	Antioxidant capacity	(Zhang et al., 2017)

process (Carmona & Michan, 2016; Ganceviciene, Liakou, Theodoridis, Makrantonaki, & Zouboulis, 2012; Lara, Sherratt, & Rees, 2016), which affects the host homeostasis and makes the host susceptible to age-associated injuries, diseases, and finally leads to death (Carmona & Michan, 2016; Moskalev, Aliper, Smit-McBride, Buzdin, & Zhavoronkov, 2014). Aging has been defined as a gradual decline in the physiological function, which is experienced by all living beings over time (de Magalhães, 2011; de Magalhães, Stevens, & Thornton, 2017; López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013; Mahmoudi & Brunet, 2012).

The worldwide population of people aged 60 years old or more was predicted to increase over sixteen percent, and twenty-one percent in 2030 and 2050, respectively (Mc Auley et al., 2017; United Nations, 2015). Even though the population of aged people increases, healthy aging is the key to avoid age-related diseases and to live a long life (Carmona & Michan, 2016). The rate of aging differs among species, populations and the organs of an individual (Carmona & Michan, 2016; Poljšak, Dahmane, & Godić, 2012).

Generally around the age of 30, intrinsic or chronological mediated aging signs are noticeable in the skin (Linder, 2012; Michniak-Kohn & Leonardi, 2017; Wulf, Sandby-Møller, Kobayasi, & Gniadecki, 2004). Extrinsic (exogenous) and intrinsic (endogenous) factors may influence skin aging. The structural changes that occur are based on physiological aging and are influenced by various environmental factors, such as unhealthy habits (smoking, consumption of junk foods and alcohol), lifestyle, the impact of heredity, and UV exposure (Ernster et al., 1995; Farage, Miller, Elsner, & Maibach, 2008; Poljšak et al., 2012). Extrinsic factors include chemicals, pollution, toxins, radiation, etc. Intrinsic factors include metabolic process, genetics and cellular metabolism (Ganceviciene et al., 2012).

Human skin cells repair the DNA damages caused by the reactive oxygen species (ROS) but eventually the cells lose their efficiency to repair the oxidative stress-mediated DNA damages and the production of ROS also increases over the rate of aging (Poljšak et al., 2012). Aging process leads to the accumulation of oxidized molecules, such as lipid peroxides, oxidized proteins and oxidative stress-mediated damaged DNA (Cutler & Mattson, 2006; Gaman, Stoian, & Atanasiu, 2011; Terman, 2001). UV radiation induces the production of free radicals in healthy skin and affects it by destroying the elastic fibers, causing dehydration, damaging the collagen, which results in the alterations of skin layer and formation of dyschromia as well as wrinkles (Gniadecka et al., 1998; Linder, 2012; Michniak-Kohn & Leonardi, 2017; Piérard, Uhoda, & Piérard-Franchimont, 2003; Tzaphlidou, 2004). Since free radicals affect the rate of aging, the administration of antioxidants can block oxidation or scavenge the production of free radicals. Thereby, the antioxidant therapy is considered to exhibit beneficial effects on the lifespan of the organism indicating the role of dietary antioxidants in longevity (Michniak-Kohn & Leonardi, 2017; Peng et al., 2014; Sadowska-Bartosch & Bartosz, 2014).

In both developing and developed countries, the aging population and aging-associated diseases are becoming the major burden in the

case of social care, and medical care (Christensen, Doblhammer, Rau, & Vaupel, 2009; Lara et al., 2016; Longo et al., 2015). Several anti-aging based therapies have been developed focusing on preventing or reversing the accumulation of altered molecules or delaying the onset of the principal biological process that is involved in the age-related progressive decline of physiological function (de Magalhães et al., 2017; Gaman et al., 2011; Ganceviciene et al., 2012).

Human longevity may be achieved by a healthy lifestyle that includes a healthy diet, consumption of antioxidants and health-promoting substances (omega 3 unsaturated FA, flavonoids, Ginkgo biloba extracts, etc.) as well as physical exercise (Rockefeller & Madeo, 2010). Healthy aging is the best way to lengthen the healthspan (Brooks-Wilson, 2013; Carmona & Michan, 2016). Therefore, the therapies that aid to obtain healthy aging is the ultimate way for the longevity in human (Kaeberlein, Rabinovitch, & Martin, 2015; Rao, 2018). Various types of fermented foods with anti-aging effects are summarized in Table 2.

The decline in the immune system is one of the signs of aging. The optimal immune activation is the best way to delay the aging process. Red wine, the most famous fermented product, contains polyphenols that promote the release of cytokines (interleukin (IL)-6, IL-10, IL-12, and IL-1 β) and immunoglobulins (IgA, and IgG) in lymphomonocytes. The consumption of a moderate level of red wine endorses the optimal expression of immune players and help decline the aging process (Magrone et al., 2008). Seo et al. (2009) investigated the anti-aging properties of rice wine using human keratinocytes and human fibroblast cells. Rice wine pretreatment encouraged the production of type I procollagen in human fibroblasts and reduced the expression of matrix metalloproteinase-1 (MMP-1) in UV-exposed fibroblasts. Rice wine also reduced the expression of TNF- α in UV-exposed human keratinocytes. The intracellular antioxidant capacity (in terms of superoxide anion scavenging capacity) of the cells increased after rice wine treatment in a dose-dependent way. The *in vivo* results suggested that rice wine increased the intracellular antioxidant capacity and exhibited potent anti-aging properties (Seo et al., 2009). Nuruk is a product consisting of un-boiled wheat grains with several active microbes. Nuruk is traditionally used as a fermentation starter to produce Korean alcoholic beverages. Antioxidant properties of the ethanolic extracts of Nuruk (different fractions; N3, N4, N5, and N6) have been studied by Lee, Cho, Kwon, Kwon, and Shin (2012c). Nuruk extract fractions exhibited ABTS scavenging activity and induced the SOD activity in H₂O₂-treated HepG2 cells. The xanthine oxidase activity was inhibited by N4 and N6. The *in vivo* results revealed that nuruk ethanolic extract fractions (N4, and N6) exhibit antioxidant properties, which can be used as a natural antioxidant source in functional foods (Lee et al., 2012c). The aqueous extract of Natto (*B. subtilis* Natto T9303 mediated fermented soybean product) supplementation extends the mean lifespan of *Caenorhabditis elegans*. The possible mechanism behind the lifespan extension of Natto supplemented *C. elegans* increased stress resistance and delayed the accumulation of lipofuscin (Ibe, Kumada, Yoshida, & Otake, 2013).

The fermented *Gastrodia elata* extracts (FGEE) exhibited antioxidant

activity. The results suggested that bioactive fractions of FGEE may be used as a natural antioxidant source in functional food products (Choi, Kim, Jung, & Suh, 2013). The composition and biological activities of fermented and non-fermented *Lespedeza cuneata* G. Don extracts were analyzed by Seong et al. (2017). The fermented *L. cuneata* G. Don extracts (FLDE) significantly inhibited the elastase, and UV-induced MMP-1 expressions in human dermal fibroblasts cells (Hs68) when compared to non-fermented *L. cuneata* G. Don extracts (NFLDE). The compound analysis revealed that the fermentation process changed the phytochemical composition of *L. cuneata* G. Don, which provided the enhanced antioxidant and antiaging activity to FLDE. The *in vivo* results suggested that FLDE can be used as a natural antioxidant source with anti-aging preparations (Seong et al., 2017). *Lb. plantarum* CGMCC8198 fermented milk supernatant (LPFM) exhibited high antioxidant capacity and may be used as a natural antioxidant source (Zhang et al., 2017).

4. Chemical nature and action mechanism of anti-aging effect and responsible compounds

Aging can be described as the natural survival reduction in living creatures due to an increase in age, which causes many changes in physiological roles and exposes them to deterioration in cardiovascular, neural, immune and hormonal functions (Pan, Lai, Tsai, Wu, & Ho, 2012). Many natural compounds from vegetables, fruits, herbs, and spices have been identified to exert anti-aging effect even though most of the observed outcomes have only been characterized through *in-vivo* studies and researches using animal models (Pan et al., 2012).

Fermentation is one of the natural ways to increase bioactive constituents in food products and also improve the proportion of nutritive against anti-nutritive compounds (Đorđević, Šiler-Marinković, & Dimitrijević-Branković, 2010). Besides, traditionally fermented food products have also been reported to possess anti-aging properties. It is therefore of great interest to identify the responsible compounds and the respective mechanisms of action. In the next paragraphs, the traditionally fermented foods that have been identified to possess anti-aging properties, along with the responsible food constituents and bacterial metabolites are presented and critically discussed.

4.1. Fermented soy products

Soybeans contain a high amount of proteins, including a famous class of flavonoid molecules, called isoflavones with two main compounds: genistein and daidzein (Pan et al., 2012). Genistein and Daidzein have been proved to increase mitochondrial biogenesis by increasing the production of peroxisome proliferator-activated receptor-gamma coactivator-1 α and sirtuin proteins (Rasbach & Schnellmann, 2008). Genistein improves insulin resistance by increasing the production of insulin receptor substrate (IRS) 1, glucose transporter (GLUT) type 1 and c-jun N-terminal kinase (Lei et al., 2011), increasing pancreatic β -cell proliferation in mice with an induced diabetic condition (Fu et al., 2010) and reducing Ab-induced mitochondrial damage by increasing superoxide dismutase activity and reducing lipid peroxidation (Xi et al., 2011). Daidzein also activates GLUT4 and IRS1 in adipocytes to increase insulin-stimulated glucose uptake (Cho et al., 2010). The fermentation process generally increases the content of genistein in soy products (Fukutake et al., 1996), thus potentially improving the anti-aging properties of soybeans. Not only that, but the anti-aging effect of soybeans might also have been caused by its high concentration effect of spermidine (Sagara, Fiechter, Pachner, Mayer, & Vollmann, 2017), bioactive polyamines with many benefits such as reversing memory loss (Gupta et al., 2013), improving blood lipid profile (Minois, Rockenfeller, Smith, & Carmona-Gutierrez, 2014), reduce cardiovascular risks mostly through inducing autophagy towards damaged cells (Eisenberg et al., 2009; Fetterman et al., 2016; Gupta et al., 2013). Highlighted products from soy such as Chungkookjang, Tempeh, and Natto are discussed as follows.

4.1.1. Tempeh

Tempeh is a traditional fermented soybean product consumed by most Indonesian people as a cheap and nutritious source of protein. It is made with dehulled, soaked, and cooked soybean inoculated with *Rhizopus* spp. (Steinkraus, Hwa, Van Buren, Provvidenti, & Hand, 1960). The fermentation process hydrolyzes proteins into amino acids and peptides, oligosaccharides into monosaccharides and phytic acid releasing inorganic phosphate (Handoyo & Morita, 2006).

There has been much attention to the health and anti-aging benefit from Tempeh recently. Total isoflavones from Tempeh were reported to reverse amnesia in rats induced by scopolamine, a known amnesia inducer, and increase cholinergic activities. This effect was caused by an increase in acetylcholine and a reduction in acetylcholinesterase levels. Tempeh isoflavones also reduced neuroinflammation in the brain better than total isoflavones from soy by decreasing the IL-1 β , a promoter to inflammatory activity, and increasing IL-10, a potent anti-inflammatory cytokine. This combination greatly showed the potency of Tempeh isoflavones in preventing and treating dementia and Alzheimer's disease (Ahmad, Ramasamy, Jaafar, Majeed, & Mani, 2014). This finding was confirmed by another study on mice which showed that Tempeh supplementation managed to increase the cognitive ability of mice and prevent oxidative damage on neurons by decreasing the levels of malondialdehyde and carbonyl protein while increasing the activities of superoxide dismutase and catalase (Chan, Lee, Wang, Yeh, & Liang, 2018). The water extract of Tempeh, especially one that was co-fermented with *Rhizopus* and *Lactobacillus*, was also found to show neuroprotective effect in BV-2 microglial cells that have been induced with lipopolysaccharides (LPS) by reducing the activity of nitric oxide synthase and the number of reactive oxygen species as well as decreasing the gene-expression of phospho-cyclic AMP response element-binding protein while increasing brain-derived neurotrophic factor gene-expression (Hwang, Wu, Wu, Shih, & Chan, 2019).

Also, Tempeh extract has shown an anti-aging effect in premenopausal and postmenopausal female rats by sustaining the quality of the uterus, improving skin quality and at the same time enhancing bone quality and strength (Safrida, Kusumorini, Manalu, & Maheshwari, 2013). Tempeh extract supplementation showed a similar level of anti-aging effects with commercial hormone therapy (genistein, ethinylestradiol, and somatotropin). This improvement was because soy isoflavones (which increased in concentration by fermentation) could replenish estrogen in postmenopausal rats and possibly enhance the quality of life of postmenopausal women (Safrida et al., 2013). Despite all these findings, further verification of Tempeh consumption efficacy on aging will be necessary since it has not been thoroughly validated through human clinical trials.

4.1.2. Chungkookjang

Chungkookjang is a fermented soybean paste from Korea which is cultured by *Bacillus* sp. bacteria with fermentation time up to 48 h. (Yoo & Kim, 2004). Soybean paste is a staple food ingredient in many Asian countries, with a difference in names and also cultures, which is used for fermentation of products such as Miso from Japan, Tauco from Indonesia and Malaysia, and Doubanjiang from China. Chungkookjang has been reported to possess higher antioxidant activity compared to regular steamed soybean and also blood-pressure-lowering capacity. Indeed, a drop of average blood pressure of 14 mmHg in just 4 h after consumption of 15 g of Chungkookjang was reported by Yoo and Kim (2004). This increase in antioxidant properties was attributed to the increase in aglycone, malonylglycoside isoflavone and total polyphenols during the fermentation process (Kwak, Lee, & Park, 2007). When Chungkookjang was fed to Sprague-Dawley rats with a high-fat diet, the activity of superoxide dismutase, an important free radical scavenger enzyme, was significantly elevated compared to that of rats that were not fed with Chungkookjang (Kwak et al., 2007). On top of its antioxidant and blood-pressure-lowering effect, the fermentation process of soybean in Chungkookjang also produced an antitumoral

lipopeptide called surfactin which repressed human breast MCF-7 cancer cells. It was also found that the longer the fermentation process, the higher the inhibitory effect (Lee et al., 2012a). These effects were confirmed with a clinical trial with overweight subjects to improve the body measurement, lipid profiles, as well as the high-sensitivity C-reactive protein of the subjects without any change in their diet (Byun, Yu, Cha, & Park, 2016). Also, supplementation of Chungkookjang was also reported to improve stroke-induced gerbils by ameliorating memory functions and other neurological indications as well as to improve glucose metabolism, reduce inflammatory inducing cytokines, and increase the gut microbiota biodiversity (Jeong et al., 2020).

4.1.3. Natto

Natto is a traditional Japanese food from soybean fermented with *Bacillus natto*. Natto is highly recognized for its anti-aging effect attributed to actions such as prevention of heart attacks, obesity, cancer, strokes, osteoporosis, intestinal sickness, and improvement of cognitive function due to old age (Cao, Liao, Wang, Yang, & Lu, 2009). A cohort study undertaken in Japan, which included more than 29,000 subjects, interestingly found that consumption of Natto may decrease the risk of mortality from cardiovascular diseases (Nagata et al., 2017). A lipopeptide biosurfactant produced during fermentation was found to prevent the adhesion against several bacteria, inhibit the growth of microbes and also reduce tumor cell viability (Cao et al., 2009). Natto water extract also significantly prolonged the lifespan of nematodes, increased their resistance to oxidative and thermal stress and delayed the accumulation of lipofuscin, a characteristic of aging cells. These findings suggested that components of Natto have a beneficial anti-aging effect and prolong life expectancy, particularly in nematodes (Ibe et al., 2013). Reduction in lifespan is often caused by oxidative stress; it has been reported that Natto exhibited an antioxidative effect, on the contrary, soybean extract did not (Ibe et al., 2013). This proves that soy fermentation greatly increased its nutrition and anti-aging capabilities, which might have been caused by antioxidative peptides, polyamines and phenolic compounds, the concentration of which increased during soybean fermentation for Natto production (Ibe et al., 2013).

4.2. Fermented dairy products

Fermented dairy products are present in almost every culture of the world and typically lactic acid-producing bacteria are used for their production. Fermentation is also thought to be one of the first ways of human-kind to preserve food, especially dairy products.

4.2.1. Yogurt

Yogurt is a type of fermented milk using mainly two types of starter culture: *Str. thermophilus* and *Lb. delbrueckii* subsp. *bulgaricus*. Yogurt is thought to possess many health benefits, such as alleviating the inability to digest lactose, reducing cholesterol, restoring microflora population in the intestine, stimulating the immune system and benefiting in cancer prevention. However, controversy still exists and further clinical trials are still necessary to establish health improvement through consuming yogurt (Desobry-Banon, Vetier, & Hardy, 1999). Human immune function tends to decline through the aging process, therefore it is important to find beneficial food that can restore it (Makino et al., 2010). Such a phenomenon was reported by Perdigon, Alvarez, Rachid, Agüero, and Gobbato (1995). In that study, rats were fed with yogurt at different intervals while intestinal tumors were induced with 1–2-dimethylhydrazine. It was found that consecutive yogurt consumption for 7 and 10 days could inhibit the growth of carcinoma in the intestines by increasing the activity of B-cells that secretes IgA, macrophages, and T-lymphocytes (Perdigon et al., 1995).

Two yogurt bacteria (*Lb. delbrueckii* subsp. *bulgaricus* and *Str. thermophilus*), when incubated with blood mononuclear cells, induced cytokines production, especially IL-1 β , TNF- α , and IFN- γ . On the contrary, the production of IFN- α and IL-2 was not induced. When analyzed

further, bacteria cell walls induced comparable cytokines production whereas cell cytoplasm did not. This finding indicated that the responsible molecules with immune-modulatory properties were present in the cell wall of bacteria. However, when an *in vivo* study was conducted, consumption of yogurt did not produce measurable human cytokines in the blood serum of volunteers. Nevertheless, there was an 85% increase in the 2'-5'A synthetase activity after yogurt consumption compared to milk consumption (Solis Pereyra & Lemonnier, 1993). Recently, yogurt consumption was reported to significantly reduce the risk of contracting common cold in elderly population, while increasing the quality of life and the activity of natural killer cells when compared to plain milk consumption (Makino et al., 2010). This anti-aging and immune-boosting effect was attributed to the bacteria polysaccharides and milk nutritional content, especially calcium, vitamin B12, and tryptophan (Makino et al., 2010).

4.2.2. Dadih

Dadhi is a dairy product from Indonesia. It is made through lactic acid fermentation of raw buffalo milk in bamboo tubes, covered with banana leaves. Fermentation takes place for 2 days until the yogurt-like texture is formed (Pato, Surono, Koesnandar, & Hosono, 2004). The micro-ecosystem that drives the fermentation is dominated by *Lactococcus* spp. followed by *Klebsiella* spp., *Lactobacillus* spp. *Bifidobacterium* spp. *Streptococcus* spp. and *Leuconostoc* spp. (Hosono, 1989; Surono, 2003; Venema & Surono, 2019). Dadhi was able to decrease blood cholesterol levels of hypercholesterolemic rats through bile acid de-conjugation in the small intestines, but this effect was only evident through Dadhi that was fermented by *Lc. lactis* subsp. *lactis* IS 10,285 and not through *Lc. lactis* subsp. *lactis* IS 2986 (Pato et al., 2004). An enzyme secreted by the bacteria, bile salt hydrolase, was responsible for the de-conjugation process. This reaction prevented bile reabsorption into the enterohepatic circulation thus increasing the fecal defecation of bile acids.

The inability of *Lc. lactis* subsp. *lactis* IS 2986 to decrease blood cholesterol level was due to its inability to colonize the lower intestinal tract, therefore it was unable to exhibit such an anti-aging effect to the hypercholesterolemic rats (Pato et al., 2004). *Lc. lactis* subsp. *lactis* IS 10,285 was, on the other hand, able to adhere to the intestinal tract, grow, and exhibit the health benefits previously discussed (Pato et al., 2004). Therefore, it can be concluded that the health benefits and anti-aging effect of such products were due to the specific bacterial strain that was able to survive through the intestinal tract and colonize in the guts.

4.3. Other types of important fermented products

4.3.1. Red yeast rice

Red Yeast Rice (RYR) is a type of food from China, traditionally made from fermenting rice and red yeast (*Monascus purpureus*). It has been used as a colorant, preservative, flavorant since the Tang Dynasty (800 CE), and as a medicine to "improve digestion, spleen, blood circulation, and resolve blood stasis" (Yang & Mousa, 2012). Recently, significant attention has been given to RYR and its cholesterol-lowering effect. Three types of research diversely explored the efficacy of RYR on cholesterol reduction in patients in Taiwan (Lin, Li, & Lai, 2005), USA (Becker et al., 2009) and Norway (Bogsrud et al., 2010). RYR managed to significantly reduce total cholesterol by 23.7% ($p < 0.001$) (Lin et al., 2005), 14.9% ($p = 0.016$) (Becker et al., 2009) and 15.5% ($p < 0.001$) (Bogsrud et al., 2010), respectively. LDL cholesterol was also significantly reduced by 23% ($p < 0.001$) (Bogsrud et al., 2010), 27.7% ($p < 0.001$) (Lin et al., 2005), and 21.3% ($p = 0.011$) (Becker et al., 2009). A recent clinical trial also confirmed that supplementation of red yeast rice managed to reduce the level of LDL-cholesterol and apolipoprotein, by 20.5% and 14.4%, respectively (Cicero et al., 2017).

The cholesterol-lowering effect of RYR was caused by Monacolin-K (Lovastatin), and a family of 8 other Monacolin compounds (Yang &

Mousa, 2012). Monacolins inhibit the rate-limiting enzyme of cholesterol synthesis in the liver, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, which in turn lower the blood cholesterol level (Gordon, Cooperman, Obermeyer, & Becker, 2010). Additionally, RYR contains sterols (campesterol, β -sitosterol, sapogenin, stigmasterol), monounsaturated fatty acids, and isoflavones that could possibly lower the cholesterol content (Yang & Mousa, 2012). However, variability in manufacturing processes may result in variability in the concentration of bioactive compounds as well as toxic ingredients such as citrinin, a potentially nephrotoxic mycotoxin (Gordon et al., 2010).

4.3.2. Kimchi

Kimchi is a fermented food from Korea, primarily made from yellow-green vegetables. Several species belonging to the *Leuconostoc*, *Lactobacillus*, and *Weissella* genera have been reported to contribute to the fermentation process, depending on the raw materials employed and the fermentation conditions (Patra et al., 2016). Several health benefits, including anticancer and antimutagenic activities, enhancement of the immune system, constipation prevention, and aging process retardation have been associated with kimchi consumption (Park et al., 2003; Park, 1995).

The anti-aging role of kimchi has been studied to some extent. Kim et al. (2011a) reported that kimchi methanolic extract exhibited an anti-aging effect against oxidative stress, which was related to human diploid fibroblasts lifespan extension along with downregulation of the genes encoding for the pro-inflammatory proteins COX-2 and iNOS. Kimchi also showed activity as an anti-cancer agent due to its β -sitosterol and a linoleic acid derivative compound (Cho, 1999). This effect was further studied and proved in a later study, in which Kimchi extract was shown to inhibit DNA synthesis of oncogenic cells by affecting the Ras signal transduction pathway (Park et al., 2003). Recently, supplementation of Kimchi showed growth reduction of HT-29 human colon carcinoma cells by increasing the mRNA and protein production of factors that could induce cell apoptosis and cell cycle arrest of the carcinoma cells (Yu, Park, Zhao, Yi, & Park, 2020).

5. Conclusion

Fermented foods demonstrate a significant anti-aging capacity which can be caused by the presence of microorganisms or by the increase in bioactive compounds produced during the fermentation processes. Some anti-aging effects that have been demonstrated are inflammation reductions, replacement of lost estrogen in menopausal period, decrease in blood pressure, increase in antioxidants, enhancement of immune function, blood cholesterol level lowering, oxidative damage protection, and cell lifespan prolonging. However, most of the anti-aging properties of fermented foods were based on *in-vitro* or *in-vivo* trials or animal models. Further clinical trials, especially ones with larger sample sizes, are still necessary to establish the efficacy of fermented foods to reverse the human aging process. The future of fermented foods seems to be upbeat, powered by the increasing awareness among the consumers in all things that are considered derived from natural sources with a health and longevity-promoting effect.

Declaration of Competing Interest

None.

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