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Review

Fermented soybean foods: A review of their functional components, mechanism of action and factors influencing their health benefits

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ABSTRACT

After thousands of years of evolution and development, traditional fermented soybean foods, with their unique charm, have gained a stable place in the global market. With the explosive development of modern biological technologies, some traditional fermented soybean foods that possess health-promoting benefits are gradually appearing. Physiologically active substances in fermented soybean foods have received extensive attention in recent decades. This review addresses the potential health benefits of several representative fermented soybean foods, as well as the action mechanism and influencing factors of their functional components. Phenolic compounds, low-molecular-weight peptides, melanoidins, furanones and 3-hydroxyanthranilic acid are the antioxidative components predominantly found in fermented soybean foods. Angiotensin I-converting enzyme inhibitory peptides and γ-aminobutyric acid isolated from fermented soy foods provide potential selectivity for hypertension therapy. The potential anti-inflammatory bioactive components in fermented soybean foods include γ-linolenic acid, butyric acid, soy sauce polysaccharides, 2S albumin and isoflavone glycones. Deoxynojirimycin, genistein, and betaine possess high activity against α-glucosidase. Additionally, fermented soybean foods contain neuroprotective constituents, including indole alkaloids, *nattokinase*, arbutin, and isoflavone vitamin B_{12}. The anticancer activities of fermented soybean foods are associated with surfactin, isolavone, furanones, trypsin inhibitors, and 3-hydroxyanthranilic acid. *Nattokinase* is highly correlated with antioxidant activity. And a high level of menaquinones-7 is linked to protection against neurodegenerative diseases. Sufficiently recognizing and exploiting the health benefits and functional components of traditional fermented soybean foods could provide a new strategy in the development of the food fermentation industry.

1. Introduction

Soybeans are recognized as an economically important crop worldwide and are a predominant source of superior-quality plant protein. Proteins, fats and carbohydrates account for approximately 36.5%, 19.9% and 30% of the raw soybeans, respectively (Vagadia et al., 2017). The proportion of fats, proteins, carbohydrates and crude fibers in soybeans is close to the proportion in meat products. Soybean products are therefore considered one of the most suitable meat product alternatives. Soybean products contain essential nutrients and some other functional ingredients, including isoflavones, bioactive peptides, saponins and phytosterols. These functional ingredients are generally used as dietary supplements due to their beneficial effects on health (Rizzo, 2020). Many epidemiological studies have demonstrated the related advantages of soybean products in lowering the risks for menopausal symptoms, cardiovascular diseases and cancers such as breast, prostate, and colon cancers (He & Chen, 2013).

Fermented soybean products are commonly used as seasoning agents or condiments to flavor foods. The fermentation process alters the physicochemical properties and enriches the organoleptic characteristics of soybean foods. The differences in these properties are dependent on the composition of the substrate, the selection of the starter culture and environmental factors (Xiang et al., 2019). Fermentation also enhances the nutritional value and functional benefits of soybean products. Microbes possess the ability to hydrolyze organic matter, improve the bioavailability of nutrients and promote the generation of bioactive components when soybeans are fermented (Lokuruka, 2011). The antinutritional factors in foods are effectively removed during

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fermentation, such as trypsin inhibitors, which inhibit nutritional uptake (Samtiya, Aluko, & Dhewa, 2020). The contents of some vitamins, such as vitamin K_2 and vitamin B_{12}, increase significantly in fermented soybean products, which is related to the metabolic properties of the starter cultures (Walther & Schmid, 2017). The bioavailability of iron and copper increases significantly during fermentation by degrading the phytates that bind with minerals (Nkhata et al., 2018). The bioavailability of isoflavone is improved by converting its glycoside forms into aglycone forms during fermentation (Araújo, Fanaro, & Villavicencio, 2013).

Currently, the consumer food demands are transitioning to a reasonable nutritional structure, namely, the scientific combination of animal proteins and vegetable proteins. Therefore, consumers are attracted to fermented soybean foods because they provide as a novel strategy to balance the dietary structure and have been widely studied worldwide due to their nutritional and health advantages (Melini et al., 2019). Consuming fermented soybeans has been reported to have multifold benefits in health, including improving the development of bone, reducing cancer risk and preventing the onset of hypertension and cardiovascular diseases. However, scientific evidence regarding the beneficial effects and the underlying mechanism for the health effects from these fermented soybean foods still need further study (Cao et al., 2018).

Traditional fermented soybean foods exhibit high nutritional value and health-promoting activities. Knowledges on the active components contributing to the functional properties of fermented soybean foods and how to effectively increased their contents through optimizing process conditions in foods are urgently needed. However, a systematic summary for the functional active components in fermented soybean foods and the processing techniques that influence the bioactive components is missing. This review focused on the studies investigating bioactive components of several representing fermented soybean foods, including high-salt fermented soybean pastes (*douchi* in China, *doenjang* in Korea and *miso* in Japan), high-salt fermented soybean curd (*sufu* in China), high-salt fermented soy sauce (soy sauce in China, *ganjang* in Korea, and *shoyu* in Japan), and short-term fermented soybean pastes (*cheonggukjang* in Korea, *natto* in Japan, and *tempeh* in Indonesia). The mechanism of action of the health-promoting components formed during soybean fermentation and the effects of the fermentation conditions on these components are explained in detail. Finally, areas for further study are briefly presented. This review has important implications for developing the soybean deep processing industry and increasing the added value of soy products and the economic benefits to some extent.

2. High-salt fermented soybean pastes

High-salt soybean pastes are semisolid viscous condiments with savory tastes that are used for preparing soups and side dishes. A few species of microorganisms are involved in the fermentation of high-salt soybean paste, including *Aspergillus spp.*, *Mucor spp.*, *Rhizopus* spp., *B. amyloliquefaciens*, *B. megaterium*, *L. fermentum* and *L. plantarum*, and yeasts, such as *C. humilis*, *Kluyveromyces lactis*, *Williopsis saturnus* and *Z. rouxii* (Kim et al., 2010). China (*douchi*), Japan (*miso*) and Korea (*doenjang*) have emerged as the leading producers of high-salt soybean pastes worldwide. *Douchi* is made from soybeans or black soybeans through fungal solid-state fermentation, followed by salting and maturation. The *douchi* manufacturing process is illustrated in Fig. 1**. A** (Fan, 2009; Nagai & Tamang, 2010). *Miso* is prepared by fermenting a mixture of steamed soybean, yeasts or lactic acid bacteria, dry salt and “koji” (Nout, 2015) (Fig. 1**. B**).*Doenjang* is traditionally prepared by mixing and fermenting moldy cooked soybeans (meju) with brine in a container, such as a porcelain pot (Kim et al., 2010) **(**Fig. 1**. C)**.

2.1. Antioxidative components

Reactive oxygen species (ROS)-induced oxidative stress is associated with the pathogenesis of several chronic diseases, including diabetes mellitus, neurodegenerative disorders, cataract development, and rheumatoid arthritis (Phaniendra, Jestadi, & Periyasamy, 2015). Compared to unfermented soybean, high-salt fermented soybean pastes enhanced antioxidant activity **(**Table 1**)**. The extracts of *douchi* exhibit antioxidant activity, which is measured by the α, α-diphenyl-β-pricrylhydrazyl (DPPH) scavenging activity and ferric-reducing antioxidant power (FRAP) assays (Xu, Du, & Xu, 2015). *Douchi* extract exhibited a preventive effect on lipid peroxidation in the liver of cholesterol-fed rats by enhancing the antioxidant enzyme activity, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) (Wang et al. 2008).

Phenolic components are biologically active components in soy foods and are mainly implicated in their antioxidant capacity. The antioxidant properties of phenolic compounds are hinged on the number and position of the hydroxyl and aromatic groups and the nature of substitutions on the aromatic rings (Costa et al., 2021). The total phenolic contents of *douchi* were relatively higher than those of other fermented soybean products, and the total phenolic content in *douchi* was 75.5% higher than the amount in unfermented soybean (Xu, Du, & Xu, 2015). Phenolic compounds in soybean are generally presented as complex insoluble

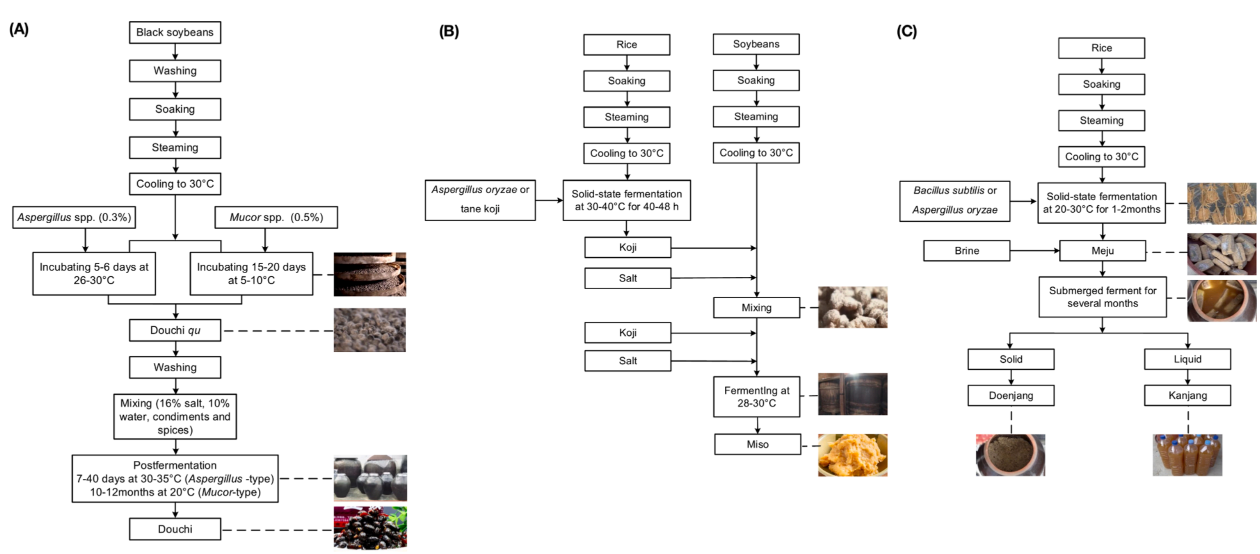

Fig. 1. **(A)** Schematic diagram of the *douchi* production process. **(B)** Schematic diagram of the *miso* production process. **(C)** Schematic diagram of the *doenjang* production process.

Table 1
Functional components in fermented soybean foods.

Fermented Soybean Foods	Functional activity	Functional Fractions or Components	Microbial species used	Effects of fermentation factors	References
High-salt fermented soybean pastes	Anti-oxidant activity	*Douchi* aqueous extract	*Aspergillus oryzae* 3.951	–	Wang et al. (2008)
		Phenolic components extracted from *douchi*	–	–	Xu, Du & Xu. (2015)
		Douchi isoflavones	*A. oryzae* 3.951	NaCl supplementation inhibited β-glucosidase activity, preventing the conversion of isoflavone glucosides to aglycones	Wang et al. (2007)
		Vanillic acid, syringic acid and ferulic acid extracted from *douchi*	*A. oryzae*	The antioxidant properties of these three phenolic compounds decreases with an increase in temperature.	Chen et al. (2005), Réblová, (2012)
		Free amino acids and low-molecular-weight peptides extracted from bacterial-type *douchi*	*Bacillus subtilis* B1	Compared with Actinomucor elegans, proteases from *B. subtilis* B1 displayed higher activity, causing the accumulation of free amino acids and low-molecular-weight peptides. Additionally, the protease at 20 h of fermentation showed the highest activity.	Fan et al. (2009)
		Douchi protein hydrolysate (10–50 kDa)	*Aspergillus* spp.	–	Wu et al. (2017)
		Melanoidin extracted from *douchi*	*A. oryzae, A. elegans*	–	Qin & Ding. (2006), Zhang, Ma & Wang. (2015)
		Total phenolic compounds, isoflavone aglycones and Maillard reaction products from *doenjang*	–	Isoflavone glycosides gradually decreased after steaming, while isoflavone aglycones distinctly increased during brining and *doenjang* aging. The contents of genistein and melanoidins prepared with 8% brine were much higher than that with 20% brine.	Lee et al. (2014), Kim, Kwak & Kim. (2018)
		HDMF and its derivatives, soy isoflavones and 4-ethylguaiacol, the products of the Maillard reaction, and low-weight peptides isolated from *miso*	*A. oryzae*	–	Chiou & Cheng. (2001)
	Anti-hypertensive activity	An ACE inhibitory peptide consisting of Phe, Ile and Gly in *douchi*	*A. egyptiacus*	The ACE inhibitory activity was reduced significantly in bacteria-type *douchi* and increased significantly in fungi-type *douchi* during the ripening process. *Douchi* fermented with *A. oryzae* exhibited the highest inhibitory activity after 30 days of maturation. The ACE inhibitory activity of *douchi* largely remains stable under high temperature and various pH conditions.	Zhang et al. (2006), Li et al. (2010), Wang et al. (2015).
		An ACE inhibitory peptide, His-Leu-Pro, isolated from *douchi*	*Mucor* spp.	–	Fan et al. (2009)
		<1 kDa fraction from *doenjang* exhibited the strongest ACE inhibitory activity		–	Kim et al. (2012)
		<5 kDa fraction of the extract from *miso*		–	Shimizu et al. (2015)
		A short peptide (His-His-Leu) isolated from *doenjang*	–	–	Shin et al. (2001)
		An ACE inhibitory peptide consisting of Ala, Phe, Leu, Glu, Gly isolated from *doenjang*	–	–	Suh et al. (1994)
		Two ACE inhibitory peptides isolated from *miso*, Val-Pro-Pro and Ile-Pro-Pro	*A. oryzae*	–	Inoue et al. 2009
		B. amyloliquefaciens isolated from *doenjang*	–	–	Kim et al. (2012)
	Anti-inflammatory and immunomodulator-y activity	γ-Linolenic acid extracted from *douchi*	*Rhizopus. oryzae*	–	Zhu & Zhang. (2013)
		γ-Linolenic acid extracted from *douchi*	*M. racemosus*	Under the optimal fermentation conditions (inoculums were 5.30 ×	Lu, Zhang & Wu. (2011)

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Table 1 (*continued*)

Fermented Soybean Foods	Functional activity	Functional Fractions or Components	Microbial species used	Effects of fermentation factors	References
				10^7 spores/10 g, 26 °C), the GLA production of *M. racemosus* was elevated	
		2S albumin protein in *miso*	–	–	Sasaki et al. (2020)
		The ethanol extract of *doenjang*	*A. oryzae*	–	Kim et al. (2014)
		Soyasaponins, genistein and daidzein in *doenjang*	*A. oryzae and B.subtilis*	The manufacturing procedures of *doenjang*, such as steaming, brining and *doenjang* aging, cause a remarkable redistribution of isoflavone isomers. The isoflavone glycosides (acetylglucosides and β-glucosides) contents decreased gradually with steaming. After brining and *doenjang* aging, all conjugate isoflavone glucosides decreased, while aglycones increased. Compared with short-term fermented soybean paste, the total flavonoid contents in long-term fermented soybean paste were much higher.	Da et al. (2021), Lee et al. (2014), Kim et al. (2018)
	Anti-α-glucosidase activity	Aqueous *douchi* extracts	*A. oryzae* 3.951, *A. elegans* 3.118 and *R. arrhizus* 3.078	*A. oryzae*-fermented *douchi qu* possessed higher activity against α-glucosidase than those fermented with *A. elegans* and *R. arrhizus. Douchi* koji made with soybean exhibited higher α-glucosidase inhibitory activity than that made with black bean. At the salt concentration of 5.0% and 7.5%, *douchi qu* displayed the highest α-glucosidase inhibitory activity. The lowest α-glucosidase inhibitory activity of *douchi* qu was at 70% relative humidity, and the highest was at 90%	Chen et al. (2007), Zhu et al. (2011), Kocevski et al. (2013)
		Deoxynojirimycin in *douchi qu*	*B. subtilis* B2	–	Zhu et al.(2011)
		Genistein detected in *douchi*	*A. oryzae* CICC 2022, *R. oryzae* CICC 3037, *M. racemosus* CICC 40491, *Tetragenococcus halophilus* CICC 10469, *Pediococcus pentosaceus* CICC 21862, *B. subtilis* CICC 10454, *B. amyloliquefaciens* CICC 10265, *B. subtilis natto* CICC 10261, *B. pumilus* CICC 10144	–	Chen et al. (2015)
		The water extract of *doenjang*	*A. oryzae* J, *M. racemosus* 42, and *B. subtilis* TKSP 24	The *doenjang* samples fermented with *A. oryzae* J, *M. racemosus* 42, and *B. subtilis* TKSP 24 at a ratio of 1: 1.5: 0.5 had the highest α-glucosidase inhibitory effects.	Chung, Rico & Kang, (2014)
		Betaine identified in *doenjang* extracts	–	–	Yang et al. (2019)
	Neuroprotective activity	*Doenjang*	–	–	Ko et al. (2019)
		Miso extract	–	–	Sakagami et al.(2018)
	Anticancer activity	*Douchi* volatile components	–	–	Guijie et al. (2021)
		Surfactin purified from the *B. subtilis* CSY19 (a *doenjang* starter)	*B. subtilis* CSY19	–	Lee et al. (2012)
		Water-soluble extracts of long-term fermented *doenjang*	–	–	Youn et al. (2016)
		Ethanol extract of *doenjang*	–	Stronger antiproliferative activity in low-salinity *doenjang.* The antitumor effects of long term fermented *doenjang* was higher than short fermented *doenjang.*	Kim, Kwak & Kim. (2018)
		8-OH-daidzein, 8-OH-genistein, daidzein and genistein isolated from *miso*	–	–	Hirota et al. (2000).
High-salt fermented soybean curd	Anti-oxidative activity	Low molecular weight peptides isolated from *sufu*	*Mucor* spp.	–	Cai et al. (2016)
		Sufu isoflavone	*A. elegans* As3.227, *M. flavus*		

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Table 1 (*continued*)

Fermented Soybean Foods	Functional activity	Functional Fractions or Components	Microbial species used	Effects of fermentation factors	References
				The contents of isoflavone glucosides in soybean cultivated in high-latitude areas were approximately 1.7-fold higher than those in soybean cultivated at low latitudes. *Actinomucor elegans* fermented *sufu* fermented under 26 °C conditions showed higher isoflavone aglycone amounts than those fermented at 32 °C. *M. flavus* fermented *sufu* at 13 °C condition was more prone to the compositional variations of isoflavone. The trend in changes of isoflavone composition gradually slowed down during the salting process.	Yin et al. (2004), Zhang et al. (2014), Yin et al. (2005), Cheng et al. (2011), Cheng et al. (2009),
	Anti-hypertensive activity	Two ACE inhibitory peptide, Ile-Phe-Leu and Trp-Leu, isolated from *sufu*	*Monascus* spp. and *Aspergillus* spp.	The salting process of *sufu*-making causes a remarkable reduction in ACE inhibitory activity. The ACE inhibitory activity was relatively higher in low-salt *sufu* and could be significantly improved under alkaline conditions.	Kuba et al. (2003), Ma et al. (2013), Ma et al. (2014)
		The extract of *sufu* containing a high proportion total hydrophobic amino acids or proline	*Mucor* spp.	–	Hang & Zhao. (2011)
		γ-Aminobutyric acid extracted from *sufu*	*K. kristinae, Lactococcus* spp., *B.licheniformis*	The salting process in *sufu* preparation is one of the main limitations in GABA content.	Bao et al. (2020), Han et al. (2001), Huang et al. (2018), Lv et al. (2020), Ma et al. (2013), Wang et al. (2015), Xie et al. (2019)
	Anti-inflammatory and immunomodulatory components	Butyric acid extracted from grey *sufu*	*Clostridium butyricum*	–	Takahashi et al. (2018)
		The protein extract of *sufu*	*Mucor* spp.	The protein extract of *sufu* with pH 6.5 and fermentation time of 6 days had the highest activation immune activity against macrophages	Liu & Zhao. (2017)
	Anti-cancer activity	*Sufu* extract	–	–	Chen et al. (2012)
High-salt fermented soy sauce	Anti-oxidative activity	4-Ethylguaiacol, catechol, daidzein and 4-ethylphenol in soy sauce	*A. oryzae*	The content of 4-ethylguaiacol was much higher under NaCl stress conditions than under the control. The content of 4-ethylguaiacol at 40 °C was 54.9% of that obtained at 30 °C incubation.	Li et al. (2017), Qi, Zhang, & Lu, (2018)
		4-hydroxy-5-methyl-3(2H)-furanone (HMF), 4-hydroxy-2,5-dimethyl-3(2H)-furanone (HDMF) and 4-hydroxy-2(or 5)-ethyl-5(or 2)-methyl-3(2H)-furanone (HDMF) in soy sauce	*Oryzae*	Supplementation of exogenous D-fructose in medium could significantly enhanced the production of HEMF and HDMF in *Z. rouxii.* With a 14-day delay to the inoculation of Z. rouxii, the content of HEMF was approximately 9-fold that of the control sample. The HEMF production capacity was also related to the variation in the salt content, total nitrogen content and pH values.	Li et al. (2017), Devanthi & Gkatzionis. (2019), Kenji et al. (2015)
		Melanoidins extracted from soy sauce	–	–	Wang et al.(2007)
		Free amino acids, total phenolic and low molecular weight (1–3 kDa) peptides in soy sauce	*A. oryzae* HN 3.042	Sonication improved anti-oxidative activity of soy sauce, which can be ascribed to the significant improvement in the levels of free amino acids, low molecular weight peptides and phenolic compounds.	Lin et al. (2016), Gao et al. (2019)
	Anti-hypertensive activity	Chinese soy sauce	–	–	Zhong et al. (2021)
		Ganjang	–	–	Mun et al. (2017)
		ACE inhibitory peptides, Ala-Trp, Gly-Trp, Ala-Tyr, Ser-Tyr, Gly-Tyr, Ala-Phe, Val-Pro, Ala-Ile, and Val-Gly, identified in *shoyu*;	–	The contents of ACE inhibitory peptides and nicotianamine were higher in soy sauce with higher	Nakahara et al. (2010)

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Table 1 (*continued*)

Fermented Soybean Foods	Functional activity	Functional Fractions or Components	Microbial species used	Effects of fermentation factors	References
		nicotianamine isolated from *shoyu*		soybean usage and short-term fermentation.	
		GABA in soy sauce	*A. oryzae*	The highest GABA content was obtained from A. oryzae NSK. Cane molasses was identified as the best substrate for GABA production. The content of GABA produced by B. cereus KBC was the highest under optimized conditions (pH 7, monosodium glutamate concentration of 5 g/L, and 40 °C).	Ab Kadir et al. (2016), Hajar-Azhari et al. (2018), Wan-Mohtar et al. (2020)
	Anti-inflammatory activity	Soy sauce polysaccharides	–	–	Kobayashi. (2010)
		Tetragenococcus halophilus Th221isolated from soy sauce	–	–	Nishimura et al. (2009)
	Neuroprotective activity	Indole alkaloids identified from *Ganjang*	–	–	Kim et al. (2016)
	Anticancer activity	Three furanones, HEMF, HDMF and HMF, from *shoyu*	–	–	Kataoka. (2005)
		Ganjang	–	The anticancer activity of *ganjang* was higher during early fermentation stage (under 5 years) than the late fermentation stage (over 10 years).	Hur et al. (2020)
Short-term fermented soybean pastes	Antioxidative activity	The peptide Ser-Phe-Glu-Trp-Val-Leu-Glu-His identified in the extract of *natto*	*B. subtilis natto*	–	Zhang et al. (2022)
		Isoflavone aglycones in *natto*	*B. subtilis* BCRC 14718, 14714, BCRC 14715 and BCRC 14716	The activity of β-glucosidase was the highest at fermentation for 12 h. The *natto* fermented with *B. subtilis* BCRC 14718 generated 57% higher isoflavone aglycones than other strains.	Li et al. (2021), Wei, Chen & Chen. (2008)
		Catechin and epicatechin of flavanol and gallic acid of phenolic acid from *cheonggukjang*	*B. subtilis CS90*	The highest phenolic acid content was reached at 60 h of fermentation.	Cho et al. (2011)
		Isoflavone aglycones from *cheonggukjang*	*B. subtilis CS90*, *B. subtilis* CSY191	The highest isoflavone aglycone content was reached at 48 h of fermentation.	Cho et al. (2011), Shin et al. (2014)
		Tempeh isoflavone	*Rhizhopus* spp.	The optimum *tempeh* process time for transformation of isoflavone glucosides into aglycones was as follows: soaking time, 6 h; cooking time, 15 min; fermentation time, 18 h. Post-cold storage < 24 h did not affect the changes in isoflavone distribution in *tempeh*	Ahmad et al. (2015), Borges et al. (2016), Ferreira et al. (2011)
		3-Hydroxyanthranilic acid isolated from *tempeh*	*Rhizopus* spp.	The concentration of HAA increased during *Rhizopus* spp. fermentation and reached the highest value after 2 days of fermentation.	Esaki et al. (1996)
		5-(δ-tocopheroxy)-δ-tocopherol	*R. oligosporus*	–	Hoppe et al. (1997)
	Anti-hypertensive activity	Five ACE-inhibitory peptides, Ile-Ile, Ile-Asp, Ile-Phe-Tyr, and Leu-Tyr-Tyr, have been identified in *natto*	*B. subtilis natto*	–	Shimakage, Shinbo & Yamada. (2012)
		Nattokinase in natto	*B. subtilis natto*	–	Kim et al. (2008)
		The extract of *cheonggukjang*	–	–	(Kim et al., 2012)
		GABA in *cheonggukjang*	–	*B. amyloloquefaciens* SRCM100730	Ryu et al. (2017)
		An ACE inhibitor peptide, Ala-Leu-Glu-Pro, identified in *tempeh*	–	–	Chalid, Hermanto, & Rahmawati. (2019)
		ACE inhibitory peptides, Ala-Val, Gly-Leu, Gly-Phe, Pro-Leu, Ala-Phe, Asp-Met, Asp-Tyr, Pro-Ala-Pro, Ile-Ala-Lys, Arg-Ile-Tyr and Val-Ile-Lys-Pro, identified in *tempeh*	–	–	Tamam et al. (2019)
		GABA in *tempeh*	*Rhizopus* spp.	The amounts of GABA in anaerobically fermented soybeans were approximately 12-fold higher than those in aerobically fermented soybeans. The maximum amounts of GABA production in *R. microsporus var. oligosporus* strains were much	Aoki et al. (2003)

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Table 1 (*continued*)

Fermented Soybean Foods	Functional activity	Functional Fractions or Components	Microbial species used	Effects of fermentation factors	References
				higher than those of other species of *Rhizopus spp*.	
	Anti-inflammatory and immunomodulatory components	Spermidine in *natto*	*B. subtilis natto*	The content of spermidine is associated with the types of *B. subtilis natto* starter culture.	Kobayashi, Shimojo & Watanabe. (2016)
		B. subtilis natto B4 spores	*B. subtilis natto* B4 spores	–	Xu et al. (2012)
		Polysaccharides from *cheonggukjang*	*B. subtilis* CS90	–	Cho et al. (2015)
		Daidzein, genistein, total polyphenol and low-molecular-weight soluble dietary fiber in *tempeh*	*R. stolonifer*	–	Sakai et al. (2006)
		Enterococcus faecalis TH10 isolated from *tempeh*	–	–	Itoh et al. (2012)
	Neuroprotective activity	*Nattokinase* in *natto*	–	–	Cásedas et al. (2019)
		Arbutin isolated in *cheonggukjang*	*B. subtilis*	The highest content of arbutin was observed at day 1	Cásedas et al. (2019)
		Tempeh isoflavone	*Rhizopus* spp.	–	Ahmad et al. (2014)
		Vitamin B_{12}	*K. pneumoniae and C. freundii*	The vitamin B_{12} level decreased with declining temperature ranging from 32 °C to 24 °C. Supplementing the culture environment with cobalt and 5,6-dimethylbenzimidazole increased the vitamin B12 level of *tempeh*.	Rooijackers, Endika & Smid. (2018), Keuth & Bisping. (1994)
	Fibrinolytic activity	*Nattokinase* in *natto*	*B. subtilis natto*	For solid-state fermentation, chickpeas were fermented with *B. amyloliquefaciens* to produce *nattokinase*. In addition, the highest yield of *nattokinase* reached 39.28 FU/g under the optimal fermentation parameters (34 °C and 50% initial moisture content). For liquid-state fermentation, the highest production (3194.25 U/ml) of *nattokinase* was achieved by *B. subtilis* after optimizing the culture medium components (Glucose, Peptone, $CaCl_2$, and $MgSO_4$). For *B. subtilis natto* WTC016, the optimum production of *nattokinase* was reached at 3284 IU/mL under the following conditions: 30 ℃, 7.0 pH, 2% inoculation volume, and 60 mL loading volume of liquid LB broth. Glutamate, metal ions and fed-batch glycerol addition are also essential for producing *nattokinase* in *B. subtilis*.	Berenjian et al. (2014), Chen & Chao. (2006), Ju et al. (2019), Wang et al. (2009). Wei et al. (2011), Deepak et al. (2008)
	Bone health	Menaquinone-7 (MK-7) in *natto*	*B. subtilis natto*	For MK-7 solid-state fermentation, under the optimal fermentation conditions (70% initial moisture, 35 °C, 4 days, 10 μL/g amylase and equal substrate mix), MK-7 production was elevated. After optimizing the addition of soybean (20 g), glycerol (40 mL/kg), mannitol (60 g/kg), yeast extract (4 g/kg), malt extract (8 g/kg), and $CaCl_2$ (4 g/kg) in the solid medium, the amount of MK-7 was increased. The optimal fermentation temperature for MK-7 production generally ranges from 37 ℃ to 45 ℃. Glycerol addition, agitation and aeration also contributed to obtaining the high concentrations of MK-7.	Kamao et al. (2007), Mahanama et al. (2011), Berenjian et al. (2011), Berenjian et al. (2015), Berenjian et al. (2012)
	Anti-cancer activity	A lipopeptide biosurfactant generated by *Bacillus natto* TK-1	*Bacillus natto TK-1*	–	Cao et al. (2009)
		The cultured supernatant of *B. subtilis* in *natto*	–	–	Zhang et al. (2019)
		Surfactin in *chungkukjang*	*B. subtilis* CSY191	–	Lee et al. (2012)
		Trypsin inhibitors	–	–	Park et al. (2013)

(*continued on next page*)

Table 1 (*continued*)

Fermented Soybean Foods	Functional activity	Functional Fractions or Components	Microbial species used	Effects of fermentation factors	References
		Genistein isolated from *tempeh*		–	Yuliani, Istyastono, & Riswanto. (2016)
		Water extract of *tempeh*		–	Hsu, Yu, & Chung. (2009
		3-hydroxyanthranilic acid isolated from *tempeh*	*Rhizopus* spp.	–	Matsuo et al. (1997)

bound esters with proteins, lipids, polysaccharides, or cell walls. The changes of fermented soybean composition are associated with many polymer-degrading enzymes, such as xylanases, amylases, and proteases (Bhanja, Kumari, & Banerjee, 2009). The free phenolic compounds are released from their bound form under the action of microbial enzymes (Salar, Purewal, & Bhatti, 2016). The bioavailability of phenolic compounds is improved through metabolism and modification, which also contributed to developing various flavors during fermentation.

Isoflavones from soybeans are mainly categorized into Daidzingroups, Genistingroups, and Glycitingroups. Each group occurs in the following four different forms: aglycones (daidzein, genistein and glycitein), β-glucoside (genistin, daidzin and glycitin), acetyl glucoside and malonyl glucoside (Yang et al., 2015). Due to its superior activity for hydrolyzing the β-glucosidic linkage of acetyl glucoside and malonyl glucoside, β-glucosidase is recognized as the critical enzyme for the biotransformation of isoflavone isomers (Yuksekdag et al., 2017). Due to the procedures use in the manufacturing of *douchi*, such as soaking, cooking and fermentation, the isoflavone isomer distribution changes remarkably. Although pre-fermentation reduced the total isoflavone levels in *douchi*, bioformation of isoflavone aglycones, particularly daidzein, genistein and glycitein, was observed. After post-fermentation, >90% of the isoflavones were in the form of aglycones in *douchi* (Wang et al., 2007). Isoflavone aglycones were suggested to possess higher antioxidant capacity and higher bioavailability than their glycosides (Lucía et al., 2017). Therefore, increased levels of isoflavone aglycone contributed to the antioxidant activity of *douchi*. Wang et al. (2007) showed that β-glucosidase activity was higher at 5% NaCl concentration. However, β-glucosidase activity was significantly inhibited at higher NaCl concentrations (7.5%, 10%, and 12.5%). This inhibited isoflavone aglycone synthesis, and the proportion of isoflavone aglycones significantly decreased when the concentration of NaCl increased from 5% to 15% (Wang et al., 2007).

The phenolic acid compounds generated during fermentation have a strong correlation with the antioxidative activity of *douchi*. Three phenolic acid compounds isolated from *douchi*, i.e., vanillic acid, syringic acid and ferulic acid, exhibited highly potent DPPH radical-scavenging activity, of which the IC_{50} values were found to be 65, 20 and 58 μM, respectively (Chen et al., 2005). Furthermore, vanillic acid and ferulic acid effectively inhibited the oxidation of soybean oil (Chen et al., 2016). The antioxidant properties of these three phenolic compounds decreases as the temperature is raised (Réblová, 2012). In bacterial-type *douchi*, low-molecular-weight peptides rather than isoflavones play a substantial role in the variations in oxidation resistance. The activity of β-glucosidase was much lower in bacterial-type *douchi* than fungi-type *douchi*. Therefore, the bioconversion of isoflavones had only marginal effects on the antioxidant potential of *Bacillus subtilis* B1-fermented *douchi*. Proteases from *B. subtilis* B1 displayed highly potent activity, causing the accumulation of free amino acids and low-molecular-weight peptides. Low-molecular-weight peptides, especially those constructed from hydrophobic, aromatic, acidic, and basic amino acids, were highly correlated with antioxidant effects (Fan et al., 2009). Analysis of each fraction in *Aspergillus*-type *douchi* protein hydrolysate revealed that the highest antioxidant content was found in the fraction with a molecular weight between 10 and 50 kDa (Wu et al., 2017). The Maillard reaction generally occurs due to the presence of reducing sugars and amino compounds in soybean and the high processing temperature during *douchi*-making. The product of the Maillard reaction, i.e., melanoidin, possesses strong antioxidative activity. The melanoidin in the long-ripened *douchiba* fermented for 18 months reached the highest concentration of 4.76% (dry basis). The melanoidin skeleton in *douchiba* has a peptide structure, which consists of Asp, Glu, Ary, Lys and Pro (Qin & Ding, 2006). The 7S subunits could be more involved in the formation of melanin during the pre-fermentation of *douchi*. And the 11S subunits could be more associated with the Millard reaction during the post-fermentation (Zhang, Ma, & Wang, 2015). The synthesis of melanoidin was influenced by reactant concentration, time, initial pH, and water activity as well as the nature and the ratio of the reactants.

Potent DPPH radical scavenging and nitrite scavenging indicate strong antioxidative activity of *doenjang*. *Doenjang* improved antioxidative defense in mice fed a high-fat diet (Chung, Rico, & Kang, 2014; Shukla et al., 2016). The antioxidative activity of *doenjang* was highly related to the contents of total phenolic compounds, isoflavones, and Maillard reaction products (Kim, Kwak, & Kim, 2018). The total phenolic content was higher in *doenjang* than in nonfermented soybean (Chai et al., 2012). *Doenjang* extracts with a higher polyphenolic compound content had stronger antioxidative activity. Correlation analysis suggested a strong positive relationship between the antioxidative activity of *doenjang* and isoflavone aglycone levels (Lee et al., 2014).

Isoflavone glycosides gradually decreased after steaming and distinctly increased during brining and *doenjang* aging (Kim et al., 2018). Additionally, increasing salt concentration decreased the isoflavone aglycones content during *doenjang* preparation; especially, the genistein content of *doenjang* prepared with 8% brine was two times higher than with 20% brine (Kim et al., 2018). The fermentation time also affects the isoflavone composition of *doenjang*. Choi et al. (2007) reported that the aglycone (daidzein and genistein) content increased to the maximum level at day 30 and then gradually decreased. At day 90, the daidzein and genistein content decreased by 12.6% and 13.4%, respectively. Changes in the daidzein and genistein content were similar to the pattern observed in β-glucosidase activity (Choi et al., 2007). Melanoidins formed in *doenjang* contributed to its increased antioxidative activity (Kwak et al., 2015). The melanoidin content was much higher in *doenjang* prepared with 8% brine (salt-reduced concentration) compared to higher NaCl concentrations. Additionally, the melanoidin content in *doenjang* increased after 3 months of aging (Kim et al., 2018).

Miso fermented with *A. oryzae* and *B. subtilis* inhibited oxidative stresses and enhanced endogenous antioxidative capacity in liver cells and kidney tissues of mice (El-Shenawy, Abu Zaid, & Amin, 2012). Phenolic molecules, including 4-hydroxy-2,5-dimethyl-3(2H)-furanone (HDMF) and its derivatives, soy isoflavones, 4-ethylguaiacol, products of the Maillard reaction, and low-weight peptides, were reported to contribute to the antioxidative activity of *miso*. In *miso* fermented with *A. oryzae*, a further increase in the daidzein and genistein content and a decrease in the daidzin and genistin content were observed after *koji* mold growth (Chiou & Cheng, 2001). Additionally, 4-hydroxy-2(or 5)-ethyl-5(or 2)-methyl-3(2H)-furanone (HEMF), an antioxidant, was detected in cooked soy *miso* (Inoue et al., 2016), and the Maillard reaction during *miso* cooking led to HEMF formation (Hayashida, Nishimura, & Slaughter, 1998).

2.2. Antihypertensive components

High-salt fermented soybean pastes generally contain relatively large amounts of salt. Although a high-salt diet is recognized as one of the most important factors for inducing the pathogenesis of hypertension, numerous studies have proven the health benefits of related products (Table 1).

The renin-angiotensin system, an indispensable humoral mechanism within the body, is consistently considered to have a prominent role in regulating blood pressure (Drenjančević-Perić et al., 2011). The angiotensin I-converting enzyme (ACE) is an essential component in the renin-angiotensin system and is responsible for high blood pressure by causing vasoconstriction by cleaving angiotensin I into angiotensin II (He, Liu, & Ma, 2013). Therefore, inhibiting ACE activity, especially through dietary antihypertensive agents, is an effective and safe strategy for controlling hypertension and reducing the risk for cardiovascular diseases. *Douchi* exhibited ACE inhibitory activity, indicating its enormous potential as a food-derived antihypertensive substance (Li et al., 2010; Zhang et al., 2006). The ACE inhibitory activity of *douchi* was primarily associated with soybean protein hydrolysis and the generation of biologically active peptides (Li-Chan, 2015). The ACE inhibitory peptide in *A. egyptiacus*-fermented *douchi* with the highest inhibited activity is composed of phenylalanine, isoleucine and glycine, which constitute approximately 10%, 20% and 50% of the peptides, respectively (Zhang et al., 2006). An ACE inhibitory peptide, His-Leu-Pro, was purified and identified in *Mucor*-type *douchi* (Fan et al., 2009). The ACE inhibitory activity of *douchi* largely remains stable under high temperature and various pH conditions (Wang et al., 2015). The stability of the ACE inhibitory activity in a high-temperature environment was linked to the thermotolerance of ACE inhibitory peptides and other biologically active components (Singh & Vij, 2018). Basic or acidic conditions promoted the proteolysis of soybean to some extent; thus structurally new peptides were released (Nishinaria et al., 2014). ACE inhibitory activity remains stable under the simulated gastrointestinal digestion of pepsin, trypsin and chymotrypsin (Wang et al., 2015). Proteases related to simulated gastrointestinal digestion, especially pepsin with lower specificity, catalyze the degradation of proteins to generate more oligopeptides and bioactive peptides. Furthermore, pepsin catalyzes the release of peptides containing hydrophobic and aromatic amino acid residues at the C-terminus by cleaving the related peptide bonds. These peptides were demonstrated to be beneficial for exerting ACE inhibitory activity (Gu & Wu, 2013). The ACE inhibitory activity varies depending on the type of starter culture. The ACE inhibitory activity was reduced significantly in bacteria-type *douchi* and increased significantly in fungi-type *douchi* during the ripening process. *Douchi* fermented with *A. oryzae* exhibited the highest inhibitory activity after 30 days of maturation (Li et al., 2010). Various microbial proteases contain specific catalytic sites acting on soybean proteins, consequently generating peptides with different structures that considerably affect the ACE inhibitory activity (Sitanggang et al., 2021).

Feeding *doenjang* promoted urinary sodium and potassium excretion and fecal potassium excretion and decreased blood pressure in SD rats fed a high-salt diet (Mun, Park, & Cha, 2019). Peptides with molecular weight below 1 kDa exhibited the strongest ACE inhibitory activity (Kim et al., 2012). After receiving an injection of the short peptide (His-His-Leu) isolated from *doenjang*, an increase in ACE-inhibitory activity in the aorta in SHRs was observed, paralleled by a decrease in systolic blood pressure (Shin et al., 2001). Another ACE inhibitory peptide isolated from *doenjang*, consisting of Ala, Phe, Leu, Glu, Gly, Ser and Asp, exerts a potential antihypertensive effect (Suh et al, 1994).

The blood pressure elevation of salt-induced hypertension with organ damage was mitigated in Dahl salt-sensitive rats fed *miso* soup for 8 weeks, which was probably induced by postponing sodium absorption in the gastrointestinal tract or by the functional components in *miso* soup (Yoshinaga et al., 2012). A dose-dependent decrease in the blood pressure levels of Dahl salt-sensitive rats was observed as the *miso* extract concentration increased. In particular, effective antihypertensive activity is observed with a $<$ 5 kDa fraction of the extract (Shimizu et al., 2015). Two short peptides identified in casein-added *miso*, i.e., Val-Pro-Pro and Ile-Pro-Pro, inhibited ACE activity, suggesting the potential protective effect of *miso* against hypertension (Inoue et al., 2009).

2.3. Anti-inflammatory and immunomodulatory components

From the perspective of traditional medicine, *douchi* is a typical herbal medicine for treating typhoid fever. As a complementary and alternative medicine, *douchi* is applied to treat heat-involved diseases, such as heartburn, inflammation and the common cold (Aum et al., 2016). Additionally, *douchi* plays a potential therapeutic role in allergic diseases related to the *T* helper cell type (*Th*) *2* immunomodulatory response, such as atopic dermatitis (AD) (Fig. 2. **A (i)**) (Jung et al., 2016). A lack of ceramides (shown at the protein kinase C (PKC) level) in the stratum corneum is one of the primary etiological factors in the pathogenesis of AD (Imokawa, 2014). Another primary characteristic of atopic dermatitis is a *Th1*/*Th2* response imbalance with a shift from *Th1* to *Th2*. This is activated by the elevation of *Th*2 cytokines, such as high levels of interleukin (*IL*)-4 in skin lesions (Wang et al., 2020). *IL*-4 promoted mast cell degranulation and the release of the associated mediator (substance P or matrix metallopeptidase 9) followed by the deterioration of AD symptoms (Sismanopoulos et al., 2012). It was confirmed that the administration of *douchi* attenuated skin injuries and improved the histological features of AD-like skin lesions in mice and decreased the *IL*-4 and PKC levels. The decreases in *IL*-4 and PKC caused decreases in inflammatory markers, such as substance P, inducible nitric oxide synthase and matrix metallopeptidase 9 (Jung et al., 2016). Hataedock treatment with *douchi* extract alleviated AD symptoms by reducing the release of inflammatory cytokines, such as Fc ε receptor, substance P, and (nuclear factor kappa B) NF-κB, during the early stage of AD. Moreover, *douchi* treatment with Hataedock promoted skin lipid barrier formation by stimulating the differentiation of keratinocytes (Kim et al., 2017).

γ-Linolenic acid (GLA 18:3, △6,9,12), an n-6 polyunsaturated fatty acid, is an essential nutrient for the human body. The metabolism of GLA drives the formation of anti-inflammatory mediators, such as leukotrienes (Wang, Lin, & Gu, 2012). The primary inflammatory cells observed in diabetic kidneys are monocytes/macrophages. Monocytes/macrophages infiltrate the target tissue, leading to renal injury, which is driven by the adhesion of molecule-1 (MCP-1) and chemokine-1 (ICAM-1) (Sara et al., 2010). GLA alleviated the renal inflammation caused by the infiltration of monocytes/macrophages by inhibiting the expression of MCP-1 and ICAM-1 (Kim et al., 2012) (Fig. 2. **A (ii)**). *R. oryzae* from *douchi* can produce large amounts of GLA (Table 1). *RoD6D*, which is highly homologous to the fungal △6-fatty acid desaturase gene, was identified in *R. oryzae*. *The* encoded product of *RoD6D* catalyzed the production of γ-linolenic acid (Zhu & Zhang, 2013). *Douchi* fermented with *M. racemosus* contains large amounts of GLA. *The* GLA content is affected by the fermentation conditions, including the microorganism used in fermentation, inoculum size, temperature and cultivation time. Under the optimal fermentation conditions (inoculums were 5.30×10^7 spores/10 g, 26 °C), the GLA production of *M. racemosus* was elevated (Lu, Zhang, & Wu, 2011).

Doenjang has been proven to have immunoregulatory effects in numerous animal and human trials (Table 1). LPS facilitates the Toll-like receptor (TLR)-4/NF-κB signaling pathway to release proinflammatory factors, such as TNF-α, *IL*-1β and *IL*-6 (Kim et al., 2012). The ethanol extract of *doenjang* exhibited an inhibitory effect on the activation of LPS-induced NF-κB in peritoneal macrophages. Furthermore, oral administration of *doenjang* significantly relieved trinitrobenzene sulfonic acid (TNBS)-induced murine colitis. *Doenjang* exerted a protective role by inhibiting inducible nitric oxide synthase, cyclooxygenase-2 (COX-2), TNF-α, *IL*-1β and *IL*-6 expression, NF-κB activation, and increasing *IL*-10 expression (Fig. 2. **B (i)**) (Kim et al., 2014). Saponins,

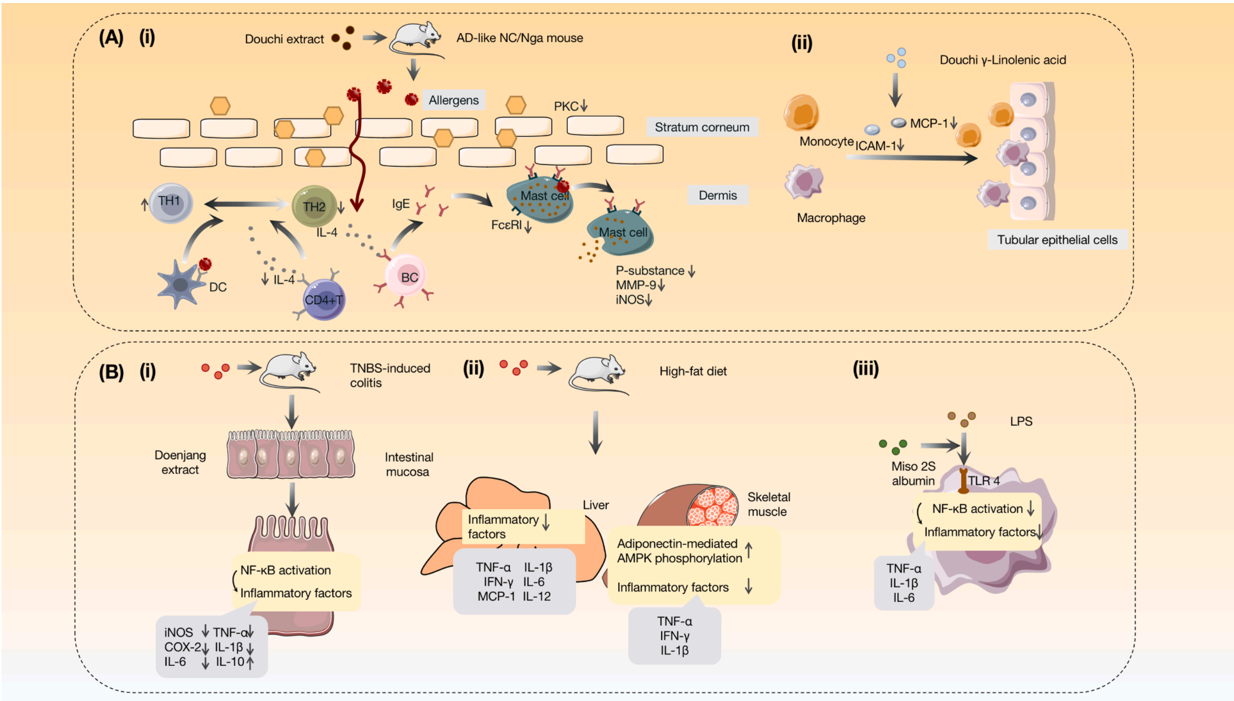

Fig. 2. (A) Proposed action mechanism of the immunomodulatory effects of *douchi* extract, γ-linolenic acid and butyrate. **(i)** *Douchi* extract inhibited the deficiency of ceramides (PKC level) in the stratum corneum and promoted *Th2* to *Th1* switching by decreasing IL-4 production. Subsequently, the the Fc ε receptor level decreased, and the release of proinflammatory cytokines (substance P, MMP-9 and iNOS) from mast cells was inhibited. **(ii)** γ-Linolenic acid isolated from *douchi* protected the kidneys by inhibiting the expression of MCP-1 and ICAM-1, which mediated the infiltration of monocytes/macrophages into the target tissue. **(B) (i)** *Doenjang* inhibited the expression of proinflammatory factors and promoted the expression of anti-inflammatory factors in TNBS-induced colitis in mice. **(ii)** Long-term fermented *doenjang* inhibited the expression of proinflammatory cytokines in the liver, promoted adiponectin-mediated AMPK activation and inhibited the expression of proinflammatory cytokines in skeletal muscle. **(iii)** *Miso* 2S albumin inhibited the activation of NF-κB in peritoneal macrophages stimulated by LPS and reduced inflammatory cytokines.

isoflavones and phytic acids are the main constituents of *doenjang* (Da et al., 2021). Among them, soyasaponins, genistin, daidzin, and their aglycone forms showed anti-inflammatory effects by suppressing the TLR4-mediated NF-κB signaling pathways (Lee et al, 2010, Morimoto et al, 2009, Seibel et al, 2009). The manufacturing procedures of *doenjang*, such as steaming, brining and *doenjang* aging, cause a remarkable redistribution of isoflavone isomers. The isoflavone glycosides (acetyl-glucosides and β-glucosides) contents decreased gradually with steaming. After brining and *doenjang* aging, all conjugate isoflavone glucosides decreased, while aglycones increased (Lee et al., 2014). In addition to the fermentation process, fermentation time is another factor affecting the immunomodulatory activity of soybean paste. Oral administration of long-term fermented soybean paste (LFSP) had a beneficial effect on the insulin resistance of mice fed a high-fat diet. Obesity triggers insulin resistance through multiple mechanisms, such as inducing chronic inflammation. High-fat diet-induced gut barrier dysfunction was recovered through treatment with LFSP, thus causing a reduction in endotoxemia and extenuating chronic inflammation. As shown in (Fig. 2**. B (ii)**), Figh LFSP treatment markedly reduced the transcript levels of proinflammatory mediators (TNFα, IFNγ, MCP1, *IL*-1β, *IL*-6 and *IL*-12) in murine liver (Kim et al., 2018). As described above, isoflavone plays multiple roles in oxidative stress and inflammation. Compared with short-term fermented soybean paste, the total flavonoid contents in LFSP were much higher, which could be explained by its bioactive activity (Kim et al., 2018).

Lipopolysaccharide (LPS) is located in the outer membrane of gram-negative bacteria. LPS generally causes mucosal inflammation, which in turn causes a breakdown in mucosal homeostasis and macroscopic damage. *Miso* is regarded as a potential dietary inhibitor of intestinal inflammation and other related diseases due to its LPS-neutralizing activity (Table 1) (Sasaki et al., 2019). The LPS-neutralizing protein in *miso* was identified as 2S albumin in soybean Fig 2**. B (iii)**. The LPS binding region is located in the 22–27 amino acid residues and 131–140 amino acid residues of the 2S albumin protein (Sasaki et al., 2020).

2.4. Components with anti-α-glucosidase activity

α-Glucosidase inhibitors commonly act as therapeutic methods for type II diabetes by inhibiting intestinal α-glucosidase and restricting postprandial carbohydrate absorption (Derosa & Maffioli, 2012). High-salt fermented soybean pastes, mainly *douchi* and *doenjang*, have been reported to possess anti-α-glucosidase activity (Table 1). The aqueous *douchi* samples collected from various regions throughout China exhibited varying degrees of anti-α-glucosidase activity, inhibiting rat intestinal α-glucosidase (Chen et al., 2007). The anti-α-glucosidase activity in *douchi* was associated with numerous factors, such as microorganisms, raw materials, additives and fermentation parameters. *A. oryzae*-fermented *douchi qu* possessed higher activity against α-glucosidase than those fermented with *A. elegans* and *R. arrhizus* (Chen et al., 2007). Under the same fermentation conditions, soybean *douchi koji* exhibited higher α-glucosidase inhibitory activity than black bean *douchi koji* (Zhu et al., 2011). For salt-added contents, *A. orzyzae*-fermented *douchi qu* displayed the highest α-glucosidase inhibitory activity at salt concentrations of 5.0% and 7.5%. This variation was most likely related to the ability of *A. orzyzae* to withstand environmental conditions with low water activity (Kocevski et al., 2013). A significant enhancement of the α-glucosidase inhibitory activity in *douchi* qu was shown during the first 48 h of fermentation. Additionally, the fermentation humidity is considered another influencing factor of anti-α-glucosidase activity. The lowest α-glucosidase inhibitory activity of *douchi* qu was at 70% relative humidity, and the highest was at 90% (Zhu et al., 2011). Deoxynojirimycin (DNJ) and some of its derivatives are potent glucosidase inhibitors (Piao et al., 2018). DNJ is detected in *douchi* qu fermented with *B. subtilis* B2 and plays a crucial role in the α-glucosidase inhibitory activity of *douchi* (Zhu et al., 2011). Additionally, the genistein found in *douchi* was considered an alternative option for α-glucosidase inhibitors in yeast. It is a well-established noncompetitive reversible α-glucosidase inhibitor (Chen et al., 2015; Yang et al, 2021). DNJ can be generated by microbial strains, such as *Bacillus* spp. DNJ synthesis is affected by media components and fermentation conditions. Yamagishi et al., (2017) showed that lactose significantly increased DNJ production at a carbon: nitrogen ratio of 6.25:1, reaching 1140 mg/L after 5 days of cultivation.

The water extract of *doenjang* shows α-glucosidase inhibitory activity. The α-glucosidase inhibitory activity of the starter culture of *doenjang* samples increases in a concentration-dependent manner and is also affected by the types and ratios of strains. Chung et al. (2014) reported that the *doenjang* sample fermented with *A. oryzae* J, *M. racemosus* 42, and *B. subtilis* TKSP 24 in a ratio of 1:1.5:0.5 showed the highest α-glucosidase inhibitory activity (67.14% ± 1.14%). Additionally, 50 mg/mL of *doenjang* showed similar α-glucosidase inhibitory activity as 2.5 mg/mL of acarbose (a standard drug). The findings show potential applications of *doenjang* for treatment of type 2 diabetes–related disorders (Chung et al., 2014). Yang et al., (2019) reported that *doenjang* extracts showed, on average, 46.3% stronger α-glucosidase inhibitory activity. Betaine identified in *doenjang* extracts shows strong α-glucosidase inhibitory activity. Acarbose and betaine inhibited α-glucosidase activity in a concentration-dependent manner: 5 mg/mL of betaine showed higher inhibition of α-glucosidase activity compared to the same concentration of acarbose (Yang et al., 2019).

2.5. Neuroprotective components

The water extract of *doenjang* shows α-glucosidase inhibitory activity. The α-glucosidase inhibitory activity of the starter culture of *doenjang* samples increases in a concentration-dependent manner and is also affected by the types and ratios of strains. Chung et al. (2014) reported that the *doenjang* sample fermented with *A. oryzae* J, *M. racemosus* 42, and *B. subtilis* TKSP 24 in a ratio of 1:1.5:0.5 showed the highest α-glucosidase inhibitory activity (67.14% ± 1.14%). Additionally, 50 mg/mL of *doenjang* showed similar α-glucosidase inhibitory activity as 2.5 mg/mL of acarbose (a standard drug). The findings show potential applications of *doenjang* for treatment of type 2 diabetes–related disorders (Chung et al., 2014). Yang et al., (2019) reported that *doenjang* extracts showed, on average, 46.3% stronger α-glucosidase inhibitory activity. Betaine identified in *doenjang* extracts shows strong α-glucosidase inhibitory activity. Acarbose and betaine inhibited α-glucosidase activity in a concentration-dependent manner: 5 mg/mL of betaine showed higher inhibition of α-glucosidase activity compared to the same concentration of acarbose (Yang et al., 2019).

2.6. Anticancer components

Table 1 summarizes the anticancer components of high-salt fermented soybean pastes. Guijie et al. (2021) showed that the volatile components of *douchi* induce apoptosis in human nasopharyngeal carcinoma CNE-1 cells. The CNE-1 cell apoptosis rate was the highest (84.6%) at a volatile-component concentration of 1.6 mg/mL; effective inhibition was also observed at concentrations of 0.4 and 0.8 mg/mL, with an apoptosis rate of 29.7% and 55.6%, respectively. In addition, caspase-3, caspase-8, caspase-9, B-cell lymphoma 2–associated X (Bax), p53, p21, E2F transcription factor 1 (E2F1), p73, and I-kappa-B-alpha (IkB-α) expression significantly increased and B-cell lymphoma 2 (Bcl-2), Bcl-xL, human inhibitor of apoptosis (HIAP)-1, HIAP-2, and nuclear factor kappa B (NF-κB) expression significantly decreased. These findings show that the volatile components of *douchi* contain numerous CNE-1 cell apoptosis–inducing compounds (Guijie et al., 2021).

B. subtilis CSY191 was isolated from *doenjang*, and surfactin, which possesses anticancer properties, was purified from *B. subtilis* CSY19 (Lee et al., 2012). Three potential surfactin isoforms possessed an identical amino acid sequence (Gly-Leu-Leu-Val-Asp-Leu-Leu). Surfactin inhibited the growth of hepatocellular carcinoma cells in a concentration-dependent manner, with a median inhibitory concentration (IC_{50}) of ~10 μg/mL at 24 h (Lee et al., 2012). Water-soluble extracts of long-term-fermented *doenjang* containing low-molecular-weight peptides at a concentration of 50 μL/mL suppressed breast cancer cells by arresting the cell cycle, inhibiting proliferation, and causing consequential apoptosis (Youn et al., 2016).The ethanol extract of *doenjang* prepared with 8% brine inhibited colorectal adenocarcinoma HT-29 cell proliferation, with a median effective concentration (EC_{50}) of 0.47 mg/mL, while the EC_{50} of *doenjang* prepared with 20% brine was 1.07 mg/mL, indicating stronger antiproliferative activity of low-salinity *doenjang* (Kim et al., 2018). To investigate the effect of aging on the anticancer activity of *doenjang*, Jung, Park, and Park (2006) fermented *doenjang* for 3, 6, and 24 months. The antitumor effects of *doenjang* fermented for 24 months was 2–3 times higher compared to *doenjang* fermented for 3 or 6 months (Jung et al., 2006).

As reported by Kono et al. (1991), intake of two cups of *miso* soup every day decreases the number of S-type colon cancer cells, and *miso* fermented for 180 days inhibited the development of azoxymethane (AOM)-induced colon cancer in F344 rats. *Miso* showed antitumorigenic effects in the breast, lung, and liver in mice (Watanabe, 2013). *Miso* consumption can also prevent liver carcinogenesis. The inhibitory effect of *miso* on liver carcinogenesis may be mediated by regulating hormonal levels, decreasing cell multiplication, and regulating angiogenesis (Sharp et al., 2005). Hirota et al. (2000) investigated the antiproliferative activity of 8-OH-daidzein, 8-OH-genistein, daidzein, and genistein isolated from *miso* toward three cancer cell lines, and 8-OH-daidzein showed the highest inhibitory activity (IC_{50} = 5.2 μM) against HL-60 cells.

3. High-salt fermented soybean curd

Sufu is a kind of high-salt fermented soybean curd with a soft, creamy, cheese-like texture and a pronounced flavor. *Sufu* can be roughly grouped into red-*sufu*, white-*sufu*, gray-*sufu* and others based on the color and flavor product characteristics. These types of *sufu* are associated with distinct ingredients during maturation. According to the types of starter, *sufu* is broadly grouped into the following three types: mold fermented *sufu*, naturally fermented *sufu* and bacteria fermented *sufu* (Wang et al., 2009). Although there are diverse methods for producing *sufu* in China, *sufu* is generally made by solid-state fermentation of tofu (soybean curd) followed by aging in brine (Fig. 3**. A**) (Fan, 2009; Nagai & Tamang, 2010**)**.

3.1. Antioxidative components

Previous studies have reported on the antioxidant activity of *sufu* extracts **(**Table 1**)**. The methanol extracts of *sufu* exhibited stronger antioxidant activity, such as DPPH radical-scavenging activity and ferric reducing power, than the nonfermented tofu extract (Cai et al., 2016).

Peptides were found to be the major contributor to the antioxidative effect in mold-fermented *sufu* extract (Wang et al., 2003). The low molecular weight peptides in white *sufu* were related to the antioxidant capacity of ABTS radical reducing power (Cai et al. 2016). The greater exposure of hydrophilic amino acids in short peptide sequences caused by proteolysis facilitated the ABTS radical cation trapping ability more compared to long peptides with less hydrophilic amino acids (Gülçin, 2010).

In general, the transformation of isoflavone glucosides to isoflavone aglycones and other metabolites occurs during the *sufu* manufacturing process, resulting in lower amounts of total isoflavones in *sufu* than in unfermented tofu. Nevertheless, the isoflavones in *sufu* are mainly present in the form of aglycones, which represent 99.7% of the total isoflavones (Yin et al., 2004). The primary factors affecting the isflavone

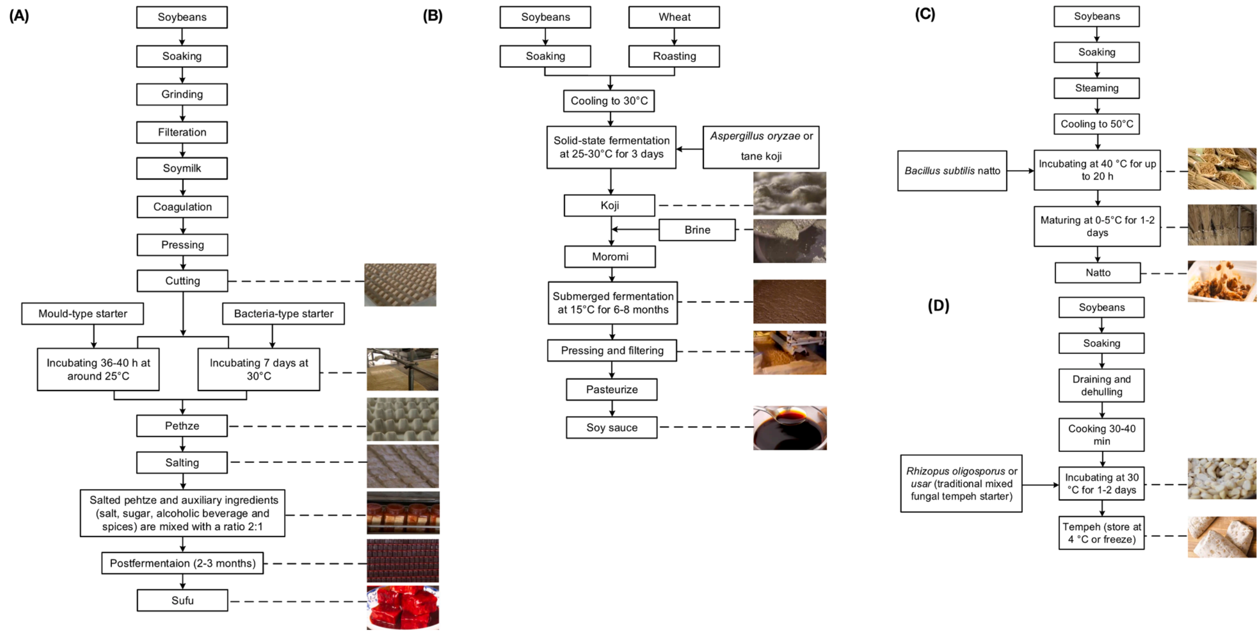

Fig. 3. **(A)** Schematic diagram of the sufu production process. **(B)** Schematic diagram of the soy sauce production process. **(C)** Schematic diagram of the *natto* production process. **(D)** Schematic diagram of the *tempeh* production process.

distribution are the types of raw materials and the fermentation parameters. There are considerable variations in the isoflavone content of soybeans depending on the cultivars used and the cultivation locations. The contents of isoflavone glucosides in soybean cultivated in high-latitude areas were approximately 1.7-fold higher than those in soybean cultivated at low latitudes (Zhang et al., 2014). Fermentation temperature is one of the most important parameters impacting the biotransformation of isoflavone and its derivatives. *Actinomucor elegans* fermented *sufu* fermented under 26 °C conditions showed higher isoflavone aglycone amounts than those fermented at 32 °C. Furthermore, in contrast to those fermented under 32 °C conditions, 6″-O-malonylglucosides were undetectable at 26 °C conditions (Yin et al., 2005). The optimal temperature range for fermenting *A. elegans* was fermented under conditions of approximately 25 °C to 30 °C. Consequently, growth at 32 °C resulted in the reduction or even loss of β-galactosidase and its activity in *A. elegans* (Han et al., 2003). Compared to *A. elegans*, *M. flavus*-fermented *sufu* can be prepared at a lower temperature (13 °C), and compositional variations in isoflavone can be observed (Cheng et al., 2011). The growth of *M. flavus*, the capacity of protease to degrade soybean protein and β-galactosidase activity were prominent at temperatures below 15 °C (Cheng et al., 2009). Furthermore, different salt levels regulate the activity of β-glucosidase in fermentation strains, which has an impact on the isoflavone content and distribution in *sufu*. For *M. flavus,* when increasing the NaCl level from 15% to 20%, the isoflavone aglycone level in *sufu* during the post-fermentation stage decreased by 23.2%, and the highest β-glucosidase activity decreased by 25.1% (Cheng et al., 2009). For *A. elegans* fermented *sufu*, the trend in changes of isoflavone composition gradually slowed down during the salting process, ascribed to the salt-inhibited β-glucosidase activity. When increasing the salt content for *sufu* processing from 30% to 38%, the β-glucosidase activity of *A. elegans* decreased by 75.4% (Yin et al., 2004).

3.2. Antihypertensive components

Hypercholesterolemia could trigger atherosclerosis and reduce arterial elasticity, thereby further aggravating hypertension (van Rooy & Pretorius, 2014). The ACE activity in the kidney and the total cholesterol level in the serum of spontaneously hypertensive rats (SHRs) fed *sufu* significantly decreased and exhibited a more pronounced antihypertensive effect compared to the control group (Kuba et al., 2003). The components with ACE inhibitory activity generated by *sufu* are summarized in Table 1.

The low-molecular-weight peptides (<10 kDa) in *sufu* exhibited ACE-inhibitory capacity, revealing potential antihypertensive activity (Wang et al., 2003). Two ACE inhibitory peptides, i.e., Ile-Phe-Leu and Trp-Leu, were identified in *sufu* extract. Both were noncompetitive inhibitors and retained a certain degree of ACE-inhibitory activity after simulated intestinal digestion (Kuba et al., 2003). Additionally, a high proportion of hydrophobic amino acids, especially Pro, were identified in the *sufu* extract with a higher ACE-inhibitory effect (Hang & Zhao, 2011). It was reported that some ACE-inhibitory peptides from soybean contained hydrophobic amino acids, such as Val-Leu-Ile-Val-Pro and Leu-Ala-Ile-Pro-Val-Asn-Lys-Pro (Mallikarjun Gouda et al., 2006; Kuba et al., 2005). The NaCl content is the principal factor influencing the ACE inhibitory activity of *sufu*, since the salting process of *sufu*-making causes a remarkable reduction in ACE inhibitory activity (Ma et al., 2013). The addition of NaCl inhibits mold growth as well as microbial protease activity, thereby reducing the production of peptides, including ACE inhibitory peptides. Another reason for the decreased ACE inhibitory activity could be the loss of water-soluble matter and the alteration of the dry matter concentration. It is worth mentioning that the ACE inhibitory activity was relatively higher in low-salt *sufu* and could be significantly improved under alkaline conditions (Ma et al., 2014).

In addition to ACE-inhibitory peptides, γ-aminobutyric acid (GABA) in *sufu* has been proven to be a potential therapeutic agent for hypertension (Hayakawa et al., 2004). Soy protein is enriched with glutamic acid, and fermentation is considered the most effective means of GABA enrichment. *Sufu* ripening requires a strictly anaerobic fermentation environment, which facilitates GABA accumulation (Ma et al., 2013). *Kocuria kristinae* is one of the dominant strains in Kedong *sufu*, a typical bacterial fermented *sufu*. Lv et al. (2020) found that GABA is synthesized via two distinct pathways in *K. kristinae*, namely, the putrescine utilization pathway and the acetylation pathway. It was also reported that *Lactococcus* spp. isolated from *sufu* displayed the capacity to synthesize GABA, such as *L. brevis*, *L. casei* and *L. curieae* (Bao et al., 2020; Han et al., 2001; Huang et al., 2018; Wang et al., 2015). Additionally, *B. licheniformis* was found to be responsible for the accumulation of

GABA in *sufu* (Xie et al., 2019). One of the main processes limiting the GABA content of sufu is the salting. This limitation could be caused by the water loss during the salting process due to the solubility of GABA (Ma et al., 2013). The synthesis of GABA by *K. kristinae* was significantly improved by adding 6% NaCl at the mid-exponential growth phase and 3% ethanol at the late exponential growth phase. Genes in synthesis pathways of GABA in *K. kristinae* were significantly regulated by optimal NaCl and ethanol conditions (Lv et al., 2020). The GABA levels of *sufu* are relatively higher (on average of 11.58 mg/g) than those of other fermented soybean foods. Among a wide variety of *sufu*, spicy *sufu* (Chubang) showed the highest level of GABA (4.84 mg/g), followed by spicy *sufu* (Tianmaren) (9.83 mg/g), *sufu* (Wangzhihe) (5.63 mg/g) and red *sufu* (Wanfang) (4.84 mg/g) (Xu, Cai, & Xu, 2017). According to the types of *sufu,* varying process strategies are applied by modifying the fermentation parameters and fermentation feedstock, naturally leading to differences in the GABA contents.

3.3. Anti-inflammatory and immunomodulatory components

Butyric acid is a short-chain fatty acid, and its anti-inflammatory action has been the subject of much attention. Butyric acid causes the downregulation of the expression of proinflammatory cytokine genes, such as *IL*-6, *IL*-8, tumor necrosis factor (TNF)-α and TGF-β, by modulating NF-κB activation. Additionally, butyric acid suppressed the differentiation of native *T* cells into major subpopulations, namely, *Th1*, *Th2* and *Th17* cells (Fig. 4. **A)** (Meijer, de Vos, & Priebe, 2010). Butyrate enemas are extensively utilized to therapeutically intervene in inflammatory intestinal disorders and other colitis-associated diseases. The positive effect of butyric acid in these diseases is primarily attributable to the regulation of energy supply in colonocytes. However, the cell signaling pathways in the butyric acid-mediated defense mechanism remain elusive (Mishiro et al., 2013). Butyric acid was the volatile organic acid with the highest content in gray *sufu*, representing approximately 58.6% of the main volatile organic acids **(**Table 1**)**. Butyric acid is much more abundant in gray *sufu* than in other foods (Ma et al., 2013). A link between the elevation of the butyric acid content in *sufu* and butyric acid-producing bacteria, such as *Clostridium butyricum,* is plausible (Takahashi et al., 2018). *C. butyricum* is known to utilize lactate to synthesize butyric acid, resulting in a higher butyric acid yield (Detman et al., 2019). Gray *sufu* possesses large amounts of butyric acid, supporting the possibility of its potential therapeutic applications in multiple diseases. An undesirable flavor is the principal limiting factor that hinders the consumption of gray *sufu.* However, it is particularly attractive for certain consumers who are accustomed to the unpleasant odorants of gray *sufu.* In *C. tyrobutyricum*, butyric acid synthesis is affected by the pH (Zhu & Yang, 2004). At pH 6.3, butyrate production was higher than at pH 6.0 and 6.7. In addition, butyric acid production decreases with decreasing pH. *C. tyrobutyricum* mainly produced acetate and lactate at pH < 5.7, with only a small amount of butyric acid. The activities of enzymes related to butyrate synthesis and lactate–pyruvate conversion were higher in *C. tyrobutyricum* at pH 6.3, while the activities of enzymes related to acetate formation and pyruvate–lactate conversion were higher in *C. tyrobutyricum* at pH 5.0 (Zhu & Yang, 2004).

Liu and Zhao (2017) reported that the protein extracts of *sufu* fermented with *Mucor* show strong immunomodulatory activity, including activating macrophages, splenocytes, and natural killer cells. The immunomodulatory activity was mediated by enhancing IL-2, interferon-γ, TNF-α, IL-1β, IL-6, inducible nitric oxide synthase (iNOS), and lysozyme secretion but inhibiting IL-4 secretion (Liu & Zhao, 2017). In addition, the fermentation time affected the immunomodulatory

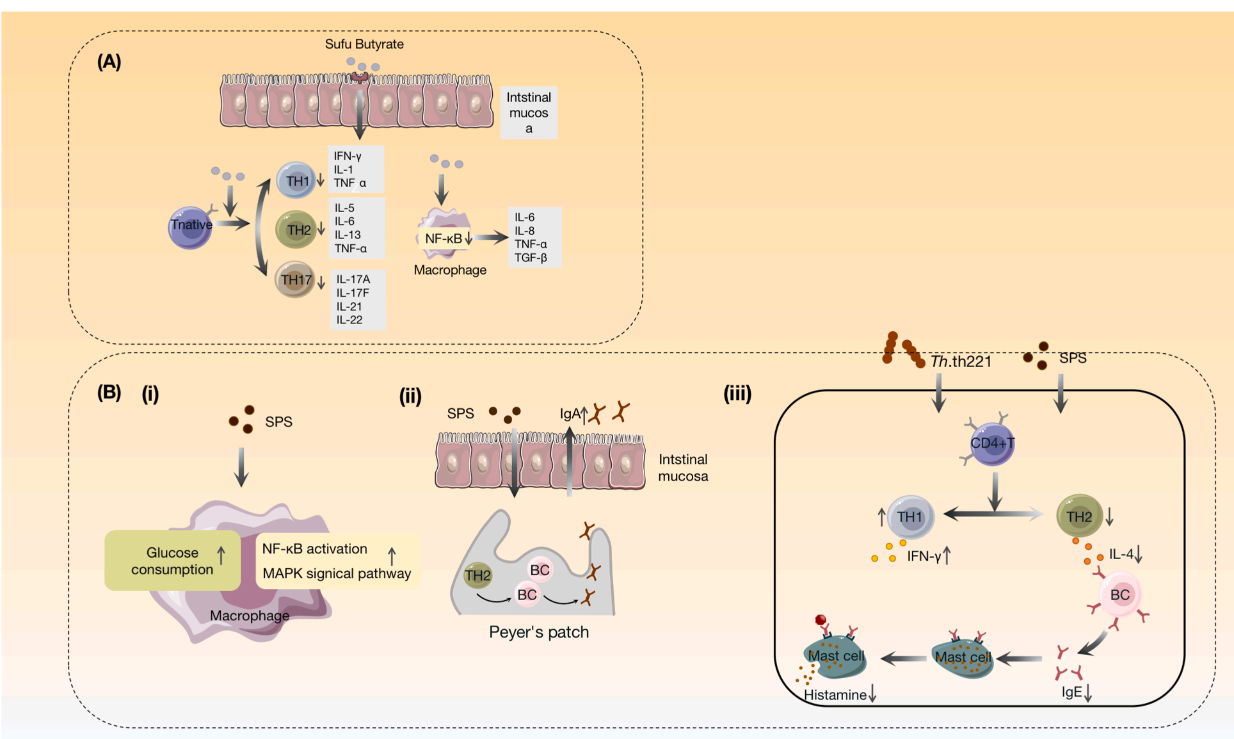

Fig. 4. (A) Butyrate isolated from sufu inhibits NF-κB and reduces inflammatory cytokines. Butyrate inhibited native T cell differentiation into *Th1*, *Th2* and *Th17 cells*. AD, atopic dermatitis; DC, dendritic cells; FcεRI, Fc ε receptor; MMP-9, matrix metallopeptidase 9; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein 1; ICAM-1, intercellular cell adhesion molecule-1; MMP-9, matrix metalloproteinase-9. **(B)** Proposed action mechanism of the immunomodulatory effects of SPS. **(i)** The consumption of glucose by peritoneal macrophages was elevated by SPS stimulation. SPS activated the NF-κB and MAPK signaling pathways in macrophages. **(ii)** SPS induced the production of IgA after crossing the intestinal epithelium. **(iii)** SPS and T. halophilus Th221 isolated from soy sauce promoted Th2 to Th1 switching by increasing IFN-γ production and decreasing IL-4 production. Subsequently, the elevation of the IgE levels was inhibited, and the release of proinflammatory cytokines (histamine) from mast cells was inhibited.

activity of *sufu*. These findings show that the protein extract of *sufu* at pH 6.5 and a fermentation time of 6 days has the highest immune activity against macrophages, which gradually decreases after 6 days.

3.4. Anticancer components

Chen et al. (2012) evaluated the antiproliferation effect of *sufu* on two human colorectal cancer cell lines (HT-29 and Caco-2). The antiproliferative effect increased with both fermentation time and concentration. As shown in Table 1, the proliferation of Caco-2 and HT-29 cells was significantly inhibited (63.52% and 62.14%, respectively) with 500 μg/mL of 16 day-*sufu* extract (Chen et al., 2012). Components of soybean, such as isoflavones, phytate, saponins, fiber, and trypsin, show anticancer activity (Lai et al., 2013). Peptides produced by hydrolysis of soybean protein or surfactins (containing cyclic peptides) or lipopeptides produced by the starter culture possess anticancer properties (Sanjukta & Rai, 2016). All these compounds can contribute to the antiproliferative effect of *sufu* on Caco-2 and HT-29 cells.

4. High-salt fermented soy sauce

Soy sauce is a fermented soybean product with a deep reddish-brown and liquid-like appearance. It serves as a condiment to improve the umami flavor and color of foods in many Asian countries. Soy sauce is produced by fermenting soybeans together with wheat or roasted grain and brine (Lioe et al., 2004). Owing to the differences in dietary habits, Asians have different preferences regarding the types of soy sauce they consume. The quality and properties of soy sauce differ depending on the dominant microbial composition, the manufacturing process, the type of raw material and the salinity of the brine. Soy sauce is categorized into three major classes according to the fermentation process, namely, high-salt liquid-state fermentation soy sauce, low-salt solid-state fermentation soy sauce and koikuchi soy sauce (Devanthi & Gkatzionis, 2019). The typical manufacturing process of soy sauce commonly involves a four-step process, as follows: *koji* production, moromi fermentation, refinement and sterilization **(**Fig. 3**. B)**. Here we mainly reviewed the bioactive compounds in high salt fermented soy sauce, including soy sauce in China, *ganjang* in Korea and *shoyu* in Japan.

4.1. Antioxidative components

Due to its potent antioxidant activity, soy sauce is a superior source of dietary antioxidants **(**Table 1**)**. As a potent antioxidant, soy sauce possesses the ability to scavenge free radicals, such as ABTS and DPPH, rapidly (Aoshima & Ooshima, 2009; Long, Kwee, & Halliwell, 2000). Dark soy sauce displayed a better ability to delay lipid peroxidation in urine and plasma than a placebo and provided a relevant contribution to repairing DNA oxidative damage (Lee et al., 2006). Adding soy sauce to beef patties effectively inhibited the formation of oxidative stress biomarkers and the discoloration induced by lipid oxidation during storage (Kim et al., 2013). The antioxidative potency of soy sauce is often linked to polyphenols, melanoidins, free amino acids and low molecular weight peptides, which play roles in diminishing oxidative damage by clearing free radicals and reactive oxygen species.

The phenolic molecules identified in soy sauce are classified as simple isoflavones, furanones, pyranones and phenolic acids. In particular, the presence of 4-ethylguaiacol, catechol, daidzein and 4-ethylphenol is responsible for the antioxidative activity of soy sauce. Additionally, 4-ethylguaiacol, catechol, daidzein and 4-ethylphenol were roughly ranked from large to small based on their contribution rates to the antioxidative activity of the soy sauce fraction (Li et al., 2017). 4-Ethylguaiacol and 4-ethylphenol have been previously demonstrated to be key odor active ingredients, and they are responsible for smoky flavor of soy sauce. Candida species, in part, contribute to the production of 4-ethylguaiacol 4-ethylphenoland, which are important sources of aroma formation (Suezawa & Suzuki, 2007). Furthermore, 4-vinylphenol and 4-vinylguaiacol could be reduced to 4-ethylphenol and 4-ethylguaiacol, respectively, through the catalysis of vinylphenol reductase. The corresponding genes were detected in *Lactobacillus plantarum* (Santamaría et al., 2018). The synthesis of 4-ethylguaiacol in *C. versatilis* can be affected by the physicochemical parameters, including the salt levels and fermentation temperature. The content of 4-ethylguaiacol was much higher under NaCl stress conditions than under the control. The content of 4-ethylguaiacol at 40 °C was 54.9% of that obtained at 30 °C incubation (Qi et al., 2018). Three isoflavone aglycones (daidzein, glycitein and genistein) were identified in soy sauce, accounting for 71% of the total isoflavone content. Additionally, daidzein was present at a higher level (56.1% of total isoflavone aglycones) (Gao et al., 2019). The substitution of raw soybeans with germinated soybeans in soy sauce preparation caused increased antioxidant activity in the FRAP assay and increased the bioavailability of isoflavone (Zhao et al., 2021). Catechol was predominantly synthesized by fungi in soy sauce; in particular, *A. oryzae.* Tryptophan was transformed into intermediate kynurenine and anthranilic acid, which was eventually transformed into catechol (Li, Zhao, & Parkin, 2011).

4-hydroxy-5-methyl-3(2H)-furanone (HMF), 4-hydroxy-2,5-dimethyl-3(2H)-furanone (HDMF) and 4-hydroxy-2(or 5)-ethyl-5(or 2)-methyl-3(2H)-furanone (HEMF) have been shown to have antioxidant activities, with the potency order of the following rank: HMF < HDMF < HEMF (Takigawa & Shibuya, 2012). Halotolerant yeast in soy sauce, such as *Zygosaccharomyces rouxii, Candida versatilis and C. etchellsii*, are responsible for the production of HEMF (Kenji et al., 2015). Exogenous D-fructose supplementation in the medium significantly improved HDMF and HEMF synthesis by *Z. rouxii* ($p < 0.001$) at 3, 5, and 7 days. Furthermore, the *HK*, *PFK1*, *G6PI*, *FBA*, *TPI*, *6GPL*, *TKT*, and *6PGDH* genes involved in HDMF and HEMF biosynthesis were differentially expressed after D-fructose supplementation (Li et al., 2020). In addition, with a 14-day delay to the inoculation of Z. rouxii, the content of HEMF was approximately 9-fold that of the control sample (Devanthi & Gkatzionis, 2019). The HEMF production capacity was also related to the variation in the salt content, total nitrogen content and pH values (Kenji et al., 2015).

The products of the Maillard reaction produce the antioxidant characteristics in soy sauce. Among them, melanoidins were the major substances of brown color products in soy sauce and showed strong antioxidant activities (Wang et al., 2007). Although the structural characteristics of melanoidins have not been completely established, carbohydrate residues could be a part of the melanoidin backbone, as observed by NMR and MS analyses (Cmmerer, Jalyschkov, & Kroh, 2002). Furthermore, amino acids could be associated with the generation of the chromophore unit, as observed by carbonyl resonance and unsaturated proton signal analyses (Gniechwitz et al., 2008). The antioxidant activity of melanoidin to some extent was ascribed to the metal chelating capacity, especially of iron. In addition, the radical-scavenging activity of melanoidin could be the other principal mechanism for its antioxidant activity (Wang et al., 2011).

Amino acids and small peptides are the main fractions of total nitrogen in soy sauce, and both accounted for 45% of the total nitrogen. A total of 31 free amino acids were detected in the soy sauce sample. The predominant free amino acids in the fermented soy sauce were proline (8.4%), leucine (7.78%) and aspartic acid (7.13%), in descending order (Lin et al., 2016). Free amino acids had effective ABTS and DPPH radical-scavenging activities and metal-ion chelating capacities. The antioxidative capacity of proteolytic products in soy sauce mostly correlated with low molecular weight (1–3 kDa) peptides. The DPPH and ABTS radical scavenging activities of soy sauce were improved nearly 1.15-fold over the control after sonication for 10 min. This can be ascribed to the significant improvement in the levels of free amino acids, low molecular weight peptides and phenolic compounds (Gao et al, 2019).

4.2. Antihypertensive components

High-salt fermented soy sauce is reported to have antihypertensive properties (Table 1). Zhong et al. (2021) reported that the administration of Chinese soy sauce (10 mL/kg) for 12 weeks significantly decreased the systolic blood pressure in Sprague–Dawley (SD) rats; significantly decreased serum renin, angiotensin II (Ang II), ACE, and aldosterone levels; regulated the Na^+ and K^+ balance; and prevented hypertension-related kidney damage (Zhong et al., 2021). *Ganjang* regulated the blood pressure in SD rats by decreasing Ang II type 1 receptor, aldosterone, mineralocorticoid receptor, and Na^+/K^+ ATPaseα1 expression and increasing Na^+ excretion (Mun et al., 2017). *Shoyu* effectively inhibited ACE activity, thereby regulating the blood pressure in SHRs and in Dahl salt–sensitive rats (Nakahara et al., 2010). Several ACE inhibitory peptides, including Ala-Trp, Gly-Trp, Ala-Tyr, Ser-Tyr, Gly-Tyr, Ala-Phe, Val-Pro, Ala-Ile, and Val-Gly, were identified in *shoyu*, and nicotianamine, an ACE inhibitory compound, was also isolated from *shoyu* (Nakahara et al., 2010). The *shoyu*-brewing process affects its ACE inhibitory activity. Nakahara et al. (2010) showed that the ACE inhibitory activity ($IC_{50} = 454$ μg/mL) of soy sauce with higher soybean usage and short-term fermentation was higher compared to regular soy sauce ($IC_{50} = 1620$ μg/mL). The concentrations of ACE inhibitory peptides and nicotianamine significantly increased, with 33-fold higher Ser-Tyr concentrations in *shoyu* produced by modified processes compared to regular soy sauce.

Enrichment of GABA content in soy sauce by fermentation has always been a research hotspot. Ab Kadir et al. (2016) investigated the GABA production in four commercial strains of *A. oryzae* (NSK, NSZ, NSJ, and NST) isolated from soy sauce *koji*, and the highest GABA content was obtained from NSK (194 mg/L). Hajar-Azhari et al. (2018) evaluated the effects of cane molasses, sugarcane syrup, and nipa syrup, used as a substrate, on GABA production by NSK: cane molasses (354.08 mg/L) was identified as the best substrate, followed by sugarcane syrup (320.7 mg/L) and nipa syrup (232.07 mg/L). Furthermore, *B. cereus* KBC, isolated from soy sauce *moromi*, produced 523.74 mg/L of GABA under optimized conditions. In another study, after optimizing conditions (pH 7, monosodium glutamate concentration of 5 g/L, and temperature 40 °C), GABA production reached 3393.02 mg/L (Wan-Mohtar et al., 2020).

4.3. Anti-inflammatory and immunomodulatory components

The immune regulation and anti-inflammation of soy sauce polysaccharides (SPS) have been reported in multiple studies (Table 1). During the fermentation of soy sauce, protein degradation occurs in the presence of microbial proteolytic enzymes, resulting in the formation of smaller peptides or free amino acids. However, polysaccharides derived from the cell wall in soy possess anti-enzymatic properties and, therefore, exist after fermentation. The cell wall polysaccharides of soybeans in soy sauce could be hydrolyzed slightly during *koji*-making and moromi fermentation (Kobayashi, 2010).

Oral administration of SPS potently exhibited passive cutaneous anaphylaxis induced by a type I hypersensitivity response in a mouse model (Kobayashi et al.,2004). Two randomized, double-blind, placebo-controlled trials showed that SPS administration was an effective treatment for sufferers with seasonal/perennial allergic rhinitis. In a 4-week, randomized, double-blind, placebo-controlled, parallel-group study, individuals with perennial allergic rhinitis received treatment with SPS. Subsequently, symptoms such as running nose and sore throat reduced (Kobayashi et al., 2004). In an 8-week randomized, double-blind, placebo-controlled, parallel-group study, individuals with seasonal allergic rhinitis caused by pollen receiving SPS treatment experienced significantly reduced symptoms, such as sneezing and nasal congestion (Kobayashi et al., 2005).

SPS possesses immunomodulatory effects in systemic immunity by activating macrophages and regulating the balance of *Th1/Th2* cell responses (Fig. 4. **B (i)**). Macrophages play diverse roles in the defense line of the innate immune system against invasive insults (Wynn & Levy, 2010). SPS increased glucose consumption in peritoneal macrophages in vitro. Mice orally administered SPS exhibited improved glucose consumption by peritoneal macrophages in vivo (Matsushita et al., 2006). SPS activated the macrophages by stimulating the NF-κB and MAPK signaling pathways, leading to the secretion of proinflammatory cytokines, such as *IL*-6 and *IL*-12 (Park, et al., 2012; Shin et al., 2021). Furthermore, SPS increased the production level of immunoglobulin A (IgA) originating from *Peyer*'s patches in vitro (Fig. 4. **B (ii)**). Orally administered SPS remarkably enhanced the concentration of IgA in the intestine in BALB/c mice (Matsushita et al., 2008). SPS isolated from traditional Korean soy sauce showed similar results both in vitro and in vivo studies (Lee & Shin, 2014). The imbalance of *Th*1/*Th*2 cytokines (*Th*2 dominance) is one of the features of allergic disorders. The biased differentiation of *Th*2 cells causes the elevation of IgE in B cells (Deo et al., 2010). Mast cell degranulation could be induced by IgE-dependent immune mechanisms (Kawa, 2012). SPS significantly suppressed the generation of *IL*-4 and the elevation of IFN-γ, thereby contributing to restoring the *Th*1/*Th*2 balance by shifting toward a *Th*1 bias (Matsushita et al., 2006). Thus, SPS favors switching off B cell IgE synthesis to regulate the Th1/Th2 balance (Fig. 4. **B (iii)**). *Tetragenococcus halophilus Th*221 in soy sauce was confirmed to contribute to the development of *Th*1-biased immune responses. *IL*-12 was generated at increased levels by mouse peritoneal macrophages after in vitro stimulation with *T. halophilus* Th221 (Fig. 4. **B (iii)**). Orally administered *T. halophilus* Th221 induced *Th*1 immune response activation and inhibited the *Th*2 response by decreasing the IgE levels in a mouse model (Masuda et al., 2008). In an 8-week, randomized, double-blind, placebo-controlled, parallel-group study, individuals with perennial allergic rhinitis were managed with oral Th221 treatment, which significantly alleviated their symptoms and decreased their serum IgE concentrations (Nishimura et al., 2009).

4.4. Neuroprotective components

Indole alkaloids identified in *ganjang* show potent antineuroinflammatory effects on LPS-induced inflammation in BV2 microglial cells (Table 1). These compounds inhibit the production of NO and prostaglandin E2, decrease nitric oxide synthase (NOS) and COX-2 expression, and inhibit the NF-κB inflammatory pathway (Kim et al., 2016).

4.5. Anticancer components

Soy sauce is also reported to have anticancer effects (Table 1). Consumption of *shoyu* inhibited benzo[a]pyrene-induced forestomach neoplasia in mice (Kataoka, 2005). Consumption of a 10% *shoyu* diet decreased the incidence and multiplicity of spontaneous liver tumors in C3H mice (Ito, Watanabe, & Basaran, 1993). Three furanones (HEMF, HDMF, and HMF) identified in *shoyu* showed anticancer activity in benzo[a]pyrene-induced mice forestomach neoplasia (Kataoka, 2005). A diet with 50 and 75 ppm HDMF significantly inhibited tumor morbidity, and HDMF had more potent effects than HMF (Kataoka, 2005). Low doses (4 mL/kg) of fermented *ganjang* exhibited strong anticancer activity against AOM/dextran sodium sulfate (DSS)-induced colonic cancer in C57BL/6J mice (Song et al., 2018). The serum was abrogated; TNF-α, IL-6, and IL-17α expression decreased; and iNOS and COX-2 expression decreased in mice fed fermented *ganjang* (Song et al., 2018). In addition, *ganjang* showed potential anticancer activity during the short- and middle-term fermentation stages (Hur et al., 2020). Compared to the long-term-fermentation group (>10 years), the anticancer activity against a panel of three cancer cell lines in the short- (<5 years) and middle-term-fermentation (5–10 years) groups was significantly enhanced (Hur et al., 2020).

5. Short-term fermented soybean pastes

Short-term fermented soybean pastes, including *natto* in Japan, *Cheonggukjang* in Korea and *tempeh* in Indonesia) are widely consumed in many Asian countries due to their flavor, aroma, and health promoting properties. *Natto* is a traditional and ethnic soybean product with a sticky texture and a faint ammonia flavor that is generally fermented by *B. subtilis natto*. *Natto* has a significant place in traditional Japanese fermented foods and is broadly consumed as a seasoning agent or condiment along with vegetables and rice. The surface of *natto* is covered with characteristic sticky substances consisting of polyglutamic acid and polyfructan. Due to its exceptional sensory characteristics, it has been difficult for *natto* to gain popularity in the international market. However, *natto* is considered a healthy food and an important dietary source of multiple micronutrients and bioactive components. *Natto* has been reported to contain abundant *nattokinase* and vitamin K_2. The former shows exceptionally potent fibrinolytic activity, and the latter plays a role in reducing the incidence of fracture and improving bone strength. A schematic diagram of the *natto* production process is shown in Fig. 3**. C** (Nout, 2015). *Cheonggukjang* is a traditional Korean dish produced by fermenting boiled soybeans rice straw, which naturally contains *B. subtilis*. Fresh *cheonggukjang* is prepared by spreading rice straw on boiled soybeans and keeping them warm at 40–50 °C for 2–3 days. *Tempeh* is an Indonesian fermented soybean product and is one of the most widely consumed fermented foods in Indonesia. Freshly prepared *tempeh* is a firm textured product covered by white mycelium with a bland, mushroom-like flavor. Multiple fungal species and lactic acid bacteria participated in the *tempeh* fermentation process. *R. oligosporus* is the dominant fungus in *tempeh* production (Efriwati et al., 2013). *The* organic acids generated by lactic and mixed acid fermentations could inhibit the growth of microorganisms capable of causing spoilage effects. Specific bacteria, such as *Klebsiella pneumoniae* and *Citrobacter freundii,* are responsible for vitamin B12 biosynthesis in *tempeh* (Rooijackers et al., 2018). A schematic diagram of the *tempeh* production process is shown in **Fig. 3. D** (Nout & Kiers, 2005; Roubos-van den Hil and Nout, 2011).

5.1. Antioxidative components

Numerous studies have investigated the functional antioxidative properties of short-term-fermented soybean pastes (Table 1). Water-soluble fractions of *natto* inhibited the oxidation of rat plasma low-density lipoprotein in vitro and decreased lipid peroxidation in the liver and aorta in cholesterol-fed rats (Iwai et al., 2002). A study of *natto*'s oxygen radical–scavenging and plasma low-density lipoprotein oxidation inhibitory activities suggested that peptides are one of the contributing factors to the antioxidative effect (Iwai et al., 2002). The antioxidative ingredients could be peptides and amino-carbonyl reactive compounds in low-molecular-weight viscous substances (Iwai et al., 2002). The peptide Ser-Phe-Glu-Trp-Val-Leu-Glu-His identified in a *natto* extract showed strong antioxidative activity (Zhang et al., 2022). β-Glucosidase is produced by *B. subtilis* during *natto* fermentation and catalyzes the formation of active isoflavones by decomposing the glucoside bond. The β-glucosidase activity in *B. subtilis* was the highest at fermentation for 12 h, and the expression levels of major genes encoding β-glucosidase (*bglH* and *bglA*) were significantly upregulated (Li et al., 2021). Under the regulation of related genes and catalysis of β-glucosidase, the contents of active isoflavones in *natto* increased by 2.2 times compared to soybean (Li et al., 2021). The starter microorganism affects the conversion between isoflavone glucoside and aglycone. *Natto* fermented with *B. subtilis* BCRC 14718 contained 57% more isoflavone aglycones compared to *natto* fermented with other *B. subtilis* strains, such as BCRC 14714, BCRC 14715, and BCRC 14716 (Wei, Chen, & Chen, 2008).

Several studies have indicated that *cheonggukjang* fermented at a later stage (40–72 h) showed higher antioxidative activity, as measured by DPPH radical–scavenging activity, ABTS radical–scavenging activity, and FRAP assays (Choi et al., 2008; Kim et al., 2011; Shin et al., 2014). The higher antioxidative activity of *cheonggukjang* could be associated with the significant increase in the total phenolic and isoflavone aglycone (daidzein, glycitein, and gensitein) content during fermentation (Shin et al., 2014). The catechin and epicatechin content of flavanol and gallic acid content of phenolic acid increased (59.6, 54.8, and 1,012 mg/kg, respectively) during *cheonggukjang* fermentation by the potential probiotic *B. subtilis* CS90, with the highest content at 60 h (Cho et al., 2011). The highest daidzein, glycitein, and gensitein content was 156.5, 10.2, and 2.5 μg/g after 48 h of fermentation, and the highest isoflavone aglycone content could be related to the highest β-glucosidase activity of the starter microorganism *B. subtilis* CSY191 (Shin et al., 2014). Similar results were reported in *cheonggukjang* fermented by *B. subtilis* CS90: the highest isoflavone aglycone content and β-glucosidase activity were found at 48 h of fermentation (Cho et al., 2011). However, Yang, Chang, & Lee (2006) reported that addition of *B. subtilis* had no effect on β-glucosidase activity and the aglycone content did not increase during *cheonggukjang* fermentation. These contrasting results indicate that the isoflavone distribution in *cheonggukjang* is significantly affected by thermal processing, soybean cultivars, the fermentation period, and the starter microorganism.

Tempeh has a protective effect on neurons against oxidative stress by activating the expression of antioxidative enzymes in vivo. Significant upregulation of antioxidant enzyme genes (SOD and CAT) in the hippocampus, striatum and cortex was observed in six-month-old senescence-accelerated mice that were administered *tempeh* (Chan et al., 2018). *Tempeh* also protected mice against alcohol-induced oxidative damage to the liver. Intake of nutrient-enriched soybean *tempeh* significantly decreased the malondialdehyde levels and increased the SOD activity and ferric reducing antioxidant power on alcohol-induced liver damage in mice (Mohd Yusof et al., 2013). The contents of isoflavone aglycones in nonfermented soybean foods are extremely low (Mani & Ming, 2017). The amounts of active ingredients from *tempeh* (Table 1), such as daidzein and genistein, were much higher than those from unfermented soybean, while their glycosides were present in relatively lower amounts (Ahmad et al., 2015). The availability of these aglycones in *tempeh* was elevated through fermentation, therefore enhancing the nutritional value of *tempeh*. The synthesis of isoflavone aglycones in *tempeh* was affected by different processing conditions. The optimum *tempeh* process time for synthesizing aglycones was as follows: soaking time, 6 h; cooking time, 15 min; fermentation time, 18 h (Borges et al., 2016; Ferreira et al., 2011). 3-hydroxyanthranilic acid (HAA), which acts as a powerful antioxidant, was identified and isolated from *tempeh* (Table 1). HAA exerted a strong antioxidant property, especially against the oxidation of soybean oil and soybean powder. The concentration of HAA increased during *Rhizopus* spp. fermentation and reached the highest value after 2 days of fermentation while exhibiting the most powerful antioxidant effect (Esaki et al.,1996). The expression of hemeoxygenase-1 (HO-1) in astrocytes was effectively activated by 3-HAA. As an antioxidant enzyme, HO-1 is generally responsible for anti-inflammation and cytoprotection. An 8-week trial conducted on C57BL6 mice administered 3-HAA confirmed the 3-HAA-mediated induction of HO-1 (Krause et al., 2011). Another antioxidative compound in *tempeh* (Table 1), i.e., 5-(δ-tocopheroxy)-δ-tocopherol, was identified based on spectroscopic analysis. This study pointed out that tocopherols existed in soy synergistically with free amino acids to enhance the antioxidant activity of *tempeh* oil during *R. oligosporus* fermentation (Hoppe et al., 1997).

5.2. Antihypertensive components

Numerous studies have shown that short-term-fermented soybean pastes possess remarkable antihypertensive properties (Table 1). Oral administration of an ACE inhibitor partially purified from *natto* (1 mg/kg body weight) significantly decreased the blood pressure in SHRs after

4 h (Ibe et al., 2009). Four ACE inhibitory peptides (Ile-Ile, Ile-Asp, Ile-Phe-Tyr, and Leu-Tyr-Tyr) were identified in *natto* (Shimakage, Shinbo, & Yamada, 2012). *Nattokinase* shows efficacy in the treatment and prevention of hypertension. In a double-blind, randomized placebo-controlled trial, participants consumed *nattokinase* (2000 FU/capsule) or a placebo capsule for 8 weeks. Both systolic and diastolic blood pressure significantly decreased after *nattokinase treatment* compared with the placebo after 8 weeks of intervention (Kim et al., 2008). In addition, 8-week consumption of *nattokinase* (2000 FU/capsule) also decreased the systolic and diastolic blood pressure in a North American population (Jensen et al., 2016). However, the mechanism underlying the suppression of hypertension by *nattokinase* is unclear, and whether *nattokinase* exerts antihypertensive effects by inhibiting ACE activity is still debatable. Studies using animal models have shown that the antihypertensive action of *nattokinase* is associated with inhibition of ACE activity (Murakami et al., 2012). However, studies in humans have shown no statistically significant differences in ACE concentrations between the *nattokinase* intervention group and the control group (Kim et al., 2008). The blood pressure–lowering action of *nattokinase* and its fragments was evaluated in SHRs. *Nattokinase* decreased the blood pressure by cleaving fibrinogen in the plasma, and the *nattokinase* fragments inhibited the increase in plasma Ang II levels (Fujita et al., 2011).

Cheonggukjang extracts can inhibit ACE activity, which varies depending on the soybean cultivars. The ACE inhibition rate of *cheonggukjang* varied between 50% and 70%, and after 48 h of fermentation at 40 °C, the ACE inhibitory activity of *cheonggukjang* was the highest (Kim et al., 2012). Cha et al. (2000) separated and purified crude extracts of *chunggugjang*, and the purified ACE inhibitory peptide was mainly composed of Ala, Phe, and His. Ryu et al. (2017), *B. amyloloquefaciens* SRCM100730 was isolated from traditional fermented food. *Cheonggukjang* fermented with *B. amyloloquefaciens* SRCM100730 had higher polyglutamic acid content and higher extracellular enzyme activity compared to commercial *chunggukjang*. Furthermore, the content of GABA, the blood pressure regulator, was three times higher compared to commercial *chunggukjang* (Ryu et al., 2017). GABA is associated with regulating cardiovascular function and the physiological blood pressure (Dhakal, Bajpai, & Baek, 2012).

GABA-enriched *tempeh* supplementation in the diet of SHRs had a mitigating effect on the elevated blood pressure compared with untreated SHRs (Aoki et al., 2003). The protein extracts of *tempeh* showed strong anti-ACE activity, indicating their potential as a functional food to prevent or alleviate hypertension. The $<$ 3 kDa fraction from protein extracts, containing a high percentage of hydrophobic amino acids (Leu, Phe, Ala, and Val), exhibited the highest ACE inhibitory activity (Chalid, Hermanto, & Rahmawati, 2019). The $<$ 3 kDa fraction in three *tempeh* samples were further filtrated and separated, and an ACE inhibitor peptide, Ala-Leu-Glu-Pro, was identified in all three samples (Tamam et al., 2019). Additionally, small peptides comprising 2–5 amino acid residues with ACE inhibitory activity were identified in *tempeh*, such as Ala-Val, Gly-Leu, Gly-Phe, Pro-Leu, Ala-Phe, Asp-Met, Asp-Tyr, Pro-Ala-Pro, Ile-Ala-Lys, Arg-Ile-Tyr, and Val-Ile-Lys-Pro (Tamam et al., 2019). The differences in production conditions, such as sanitation, may affect the microbiota involved in *tempeh* fermentation, which, in turn, affects biofunctional peptide formation. In addition, the blanching process is more conducive to obtaining bioactive peptides. Blanching changes the soybean tissue structure, including cell membrane destruction and increased cell wall porosity. As a result, the hyphae of trichospora easily penetrate the cotyledons of soybean and secrete proteases to break up more proteins into peptides. The GABA content of *tempeh* is considerably changeable during *tempeh* fermentation. The process conditions and microorganism strain used in fermentation are predominant factors that affect the GABA content. For instance, the GABA content in anaerobically fermented soybean was approximately 12-fold higher compared to aerobically fermented soybean (Aoki et al., 2003). Yusof et al. (2013) increased the levels of free amino acids (including GABA) and peptides in the *tempeh* product using anaerobic fermentation (30 °C for 30 h) after fermenting soybean with *Rhizopus* spp. 5351 for 30 h at 30 °C. Watanabe et al. (2007) also increased the GABA content using anaerobic fermentation for 5 h after fermenting soybean with *R. microsporus* for 20 h. Additionally, the maximum GABA production in *R. microsporus* var. *oligosporus* strains was much higher compared to other *Rhizopus* spp. (Aoki et al., 2003).

5.3. Anti-inflammatory and immunomodulatory components

Many studies have shown that short-term-fermented soybean pastes have anti-inflammatory and immunomodulatory effects (Table 1). Spermidine showed anti-inflammatory and immune regulatory activity (Liu et al., 2020; Carriche et al., 2021). Fermented *natto* is a good source of spermidine. The fermentation process led to a 41.1% increase in spermidine in *natto* compared to raw soybean (Kobayashi, Shimojo, & Watanabe, 2016). Spermidine was generated using *B. subtilis natto* in *natto* production (Kim, Byun, & Mah, 2012). Due to the catalysis of polyamine-degrading enzymes in *B. subtilis* (Kobayashi et al., 2017), the polyamines in *natto* might degrade during storage. Therefore, the spermidine content in fresh samples was higher compared to *natto* products stored in markets (Nishibori, Fujihara, & Akatuki, 2007). The spermidine content is associated with the types of *B. subtilis* (*natto*) starter culture. In one study, the starter culture had little impact on the putrescine and spermine content but affected the spermidine content (Kobayashi et al., 2016). Spermidine shows some cytotoxicity. However, the spermidine content in *natto* is much lower than that at which it exerts cytotoxicity (Del Rio et al., 2018). Therefore, there is insufficient evidence to prove whether spermidine in *natto* has a harmful effect on health.

B. subtilis natto, a probiotic starter for *natto* fermentation, shows anti-inflammatory and immunomodulatory activity. *B. subtilis natto* B4 spores activated macrophages by upregulating acid phosphatase and lactate dehydrogenase activity. Additionally, the spores contributed to immune regulation by increasing iNOS activity and cytokine (TNF-α, interferon-γ, IL-1β, IL-6, IL-12, IL-10, and macrophage inflammatory protein-2) generation (Xu et al., 2012). Oral administration of *B. subtilis natto* BS04 had a beneficial effect on cellular immunity in BALB/C mice by enhancing the cytotoxic activity of natural killer cells and phagocytosis by the mononuclear phagocyte system (Gong et al., 2018). In addition, *B. subtilis natto* had similar immunomodulatory effects with *Lactobacillus* and *Bifidobacterium* (Park et al., 1999; Morita et al., 2002). However, due to the higher thermal resistance of *B. subtilis natto* B4 spores, *B. subtilis natto* has greater potential in applications in the food industry.

Cheonggukjang showed anti-inflammatory activity by inhibiting NF-κB activation and increasing the expression levels of NF-κB-targeting genes (*COX-2* and *iNOS*) and vascular cell adhesion molecule (VCAM) in the kidneys of rats fed a high-fat diet (Choi et al., 2011). *Cheonggukjang* also showed anti-inflammatory activity by regulating the expression levels of pro-inflammatory cytokines genes (*MCP-1*, *TNF-α*, and *IL-6*) in the liver of C57BL/6 mice fed a high-fat diet (Park, Kim, & Moon, 2011). In addition, the polysaccharides from *cheonggukjang* showed immunoregulatory activity by activating the complement system and enhancing NO and immunostimulatory cytokine production (IL-6 and IL-12) in vitro (Cho et al., 2015). These polysaccharides had protective effects on immunosuppression in Cy-treated mice, resulting in the restoration of lymphocyte proliferation, native killer cell activity, and leukocyte count (Cho et al., 2015).

The aqueous extract of nutrient-enriched *tempeh* (NESTE) showed anti-inflammatory activity on the LPS-treated mouse macrophage cell line: 5 mg/mL of NESTE significantly inhibited NO, IL-1β, and TNF-α production without any cytotoxicity (Yusof et al., 2019). Compared to raw soybean, a high content of bioactive compounds, including antioxidants, GABA, and phenolic acids, was found in the NESTE extract produced by fermentation with the *Rhizopus* 5351 strain (Ali et al., 2016). These bioactive compounds were reported to possess anti-inflammatory properties (Kassim et al., 2010; Auteri, Zizzo, & Serio, 2015; Wu et al., 2016). However, the detailed mechanism of active compounds isolated from NESTE that improve anti-inflammatory activity requires further study.

Aoki et al. (2020) reported that *tempeh* fermented with *R. stolonifer* had immunomodulatory effects on AD-like skin lesions induced by the house dust mite in NC/Nga mice. *Tempeh* fermented with *R. stolonifer* alleviated skin severity and decreased plasma IgE concentration in the mice (Aoki et al., 2020). Sakai et al. (2006) identified four bioactive compounds (0.024% daidzein, 0.041% genistein, 0.35% total polyphenol, and 2.5% low-molecular-weight soluble dietary fiber) in *tempeh* fermented with *R. stolonifer*. Genistein (20 mg/kg) consumption by spontaneous AD–developing NC/Nga mice significantly inhibited the development of dermatitis (Sakai et al., 2006). A cocoa diet (containing 0.2% polyphenols) prevented antiallergen IgE synthesis in young rats (Abril-Gil et al., 2012). Additionally, consumption of soluble dietary fibers (5%), such as pectin, chitosan, and glucomannan, decreased the IgE concentration in rat plasma (Sahasrabudhe et al., 2018). The decreased in the plasma IgE concentration could be associated with the polyphenols and low-molecular-weight soluble dietary fiber in *tempeh*. Aoki et al. (2020) evaluated the content of bioactive components (isoflavone aglycone, total polyphenol, and low-molecular-weight soluble dietary fiber) in *tempeh* fermented with *R. oligosporus*, *R. oryzae*, or *R. stolonifer*. Results showed that *tempeh* fermented with *R. stolonifer* had the highest content of bioactive components (Aoki et al., 2020). *Tempeh* fermented with *R. stolonifer* increased the abundance of cecal *Bifidobacterium* and *Lactobacillus* in the cecum of rats, increasing cecal propionate and butyrate levels (Lührs et al., 2002). Propionate and butyrate have been proven to have preventive effects on inflammatory bowel diseases (Sun et al., 2017). Heat-killed *Enterococcus faecalis* TH10 isolated from *tempeh* stimulated NO in murine macrophage cells by activating the the TLR2-TLR1/6 pathway, facilitating host immunomodulation (Itoh et al., 2012). Excessive NO production promotes the development of inflammatory diseases. *E. faecalis* TH10 stimulated the immunomodulation of macrophage cells, albeit to a distinctly lesser degree than that caused by LPS stimulation, and a moderate activation of macrophage cells stimulated by *E. faecalis* TH10 benefited the health of the host (Itoh et al., 2012).

5.4. Neuroprotective compounds

Short-term-fermented soybean pastes also contain neuroprotective compounds, which help prevent diseases such as neurodegenerative disorders (Table 1). Pan et al. (2009) reported that dietary supplementation with *natto* (16 mg/day) for 1 week improved the neurobehavioral deficits after sciatic nerve injury in rats. The mechanism underlying *natto* promoting peripheral nerve regeneration was mediated by catalyzing the clearance of fibrin and reducing TNF-α production. *Natto* treatment significantly ameliorated the destruction of the blood–brain barrier and attenuated TNF-α production and cell apoptosis induced by sciatic nerve crush injury (Pan et al., 2009). Amyloid fibrils, closely related to AD, were effectively degraded by *nattokinase* both in vitro and in vivo, indicating the potential role of *nattokinase* in treating AD (Hsu et al., 2009; Girigoswami et al., 2019). Nanonutraceuticals containing *nattokinase* reversed colchicine-induced cognitive impairment in rats: *nattokinase* exerted neuroprotective effects by inhibiting Aβ and BACE-1 activity (Bhatt et al., 2018). After treatment with *nattokinase* at a dose of 360 FU/kg, cholinesterase activity and transforming growth factor (TGF)-β, IL-6, and p53 levels significantly decreased, with a concomitant increase in Bcl-2 levels compared to the control group (Ahmed et al., 2013). *Nattokinase* exerted its neuroprotective function through its proteolytic, anti-inflammatory, and antiapoptotic effects (Ahmed et al., 2013). *Nattokinase* also had neuroprotective effects against focal cerebral ischemia in gerbils (Wang et al., 2012). *Nattokinase* consumption at a low dose (4 mg/day) for 7 days significantly changed fibrinolytic activity and reduced infarct volumes (Wang et al., 2012). In addition, *nattokinase* had neuroprotective effects during brain ischemia by inhibiting platelet activation, suppressing apoptosis, relaxing vascular smooth muscle, and restoring the endothelial thrombofibrinolytic balance (Ji et al., 2014).

Cheonggukjang fermented with a mixed culture of *B. subtilis* MC31 and *L. sakei* 383 had beneficial effects on TMT-induced neurotoxic damages in the hippocampus of mice (Go et al., 2016). Compared to the control group, the *cheonggukjang*-pretreated group showed amelioration of memory loss in a dose-dependent manner. Acetylcholinesterase (AChE) is the active form of caspase-3. *Cheonggukjang* inhibited AChE and superoxide dismutase activity (Go et al., 2016). *Cheonggukjang* fermented with *B. amyloliquefaciens* MJ1-4 and *Bacillus* sp. EMD17 protected murine hippocampus neuronal (HT22) cells against glutamate-induced oxidative stress damage (Woo et al., 2014). Arbutin isolated from *cheonggukjang* inhibited tyrosinase activity by reacting competitively with L-tyrosine. Tyrosinase inhibitors possess neuroprotective effects, contributing to the treatment and prevention of neurodegenerative diseases, such as Parkinson's disease (Cásedas et al., 2019). In one study, the highest content of arbutin was observed at day 1, which decreased afterward (Jin, Jeon, & Mah, 2020). Although arbutin was gradually degraded by *B. subtilis*, tyrosinase inhibitory activity increased as fermentation proceeded, due to the presence of other tyrosinase inhibitory compounds in *cheonggukjang* (Jin, Jeon, & Mah, 2020).

Several studies have shown the potential for the neuroprotective effects of *tempeh*. Acetylcholinesterase (AchE) is the protein contributing to the hydrolysis of the neutransmitter acetylcholine (Ach) in nervous system synapses. Decreased Ach levels in the brains of Alzheimer's disease patients were strongly associated with dementia onset (Campanari et al., 2013). Soybean isoflavone has a modulatory effect on the cholinergic system and neuronal function by inhibiting AChE to elevate ACh levels (Cong et al., 2018) **(**Fig. 5**.** A **(i))**. Among soybean isoflavones, daidzein is crucial for ACh synthesis due to its ability to activate choline acetyltransferase (Heo et al., 2006). Oral administration of isoflavone from *tempeh* for 15 days reversed scopolamine-induced memory impairment in rats by regulating the cholinergic blockade of inflammation. The isoflavones from *tempeh* at different concentrations all significantly increased Ach and reduced AchE levels. However, significant improvement of isoflavone in cholinergic activities can be observed only at high concentrations (Ahmad et al., 2014). Another pathogenic mechanism that causes memory loss due to neurodegeneration is neuroinflammation. Microglia and astrocytes can release proinflammatory cytokines and reactive oxygen species, which leads to apoptosis and necrosis in neurons (Cong et al., 2018). A neuroinflammation study was conducted on rats fed isoflavone from *tempeh*. The results indicated that isoflavone from *tempeh* exhibited better inhibition of neuroinflammation than that from soybeans. Isoflavone suppressed the activity of COX-1 and COX-2, attenuated the *IL*-1β levels and enhanced the *IL*10 levels in the brain with Alzheimer's disease, which contributed to preventing neuroinflammation (Ahmad et al., 2014) **(**Fig. 5**. A (ii))**.

Vitamin B_{12} (cobalamin) is essential for nervous system maintenance, effective erythropoiesis, and cell metabolism (Honzik et al., 2010; Lachner, Steinle, & Regenold, 2012). Vitamin B_{12} is biosynthsized in considerable amounts during *tempeh* fermentation. Unexpectedly, *R. oligosporus* or lactic acid bacteria are not in charge of the biosynthesis of vitamin B_{12}. Vitamin B_{12} is actually generated by occasional contaminants, such as *K. pneumoniae* and *C. freundii*, during the fermentation process (Rooijackers, Endika, & Smid, 2018). Vitamin B_{12} formation by *K. pneumoniae* and *C. freundii* isolated from *tempeh* was affected by the fermentation conditions. The vitamin B_{12} level decreased with declining temperature ranging from 32 °C to 24 °C. Supplementing the culture environment with cobalt and 5,6-dimethylbenzimidazole increased the vitamin B12 level of *tempeh* (Keuth & Bisping, 1994). Kustyawati et al. (2020) assessed the association between the starter culture and vitamin B12 content during *tempeh* production. The highest vitamin B_{12} level

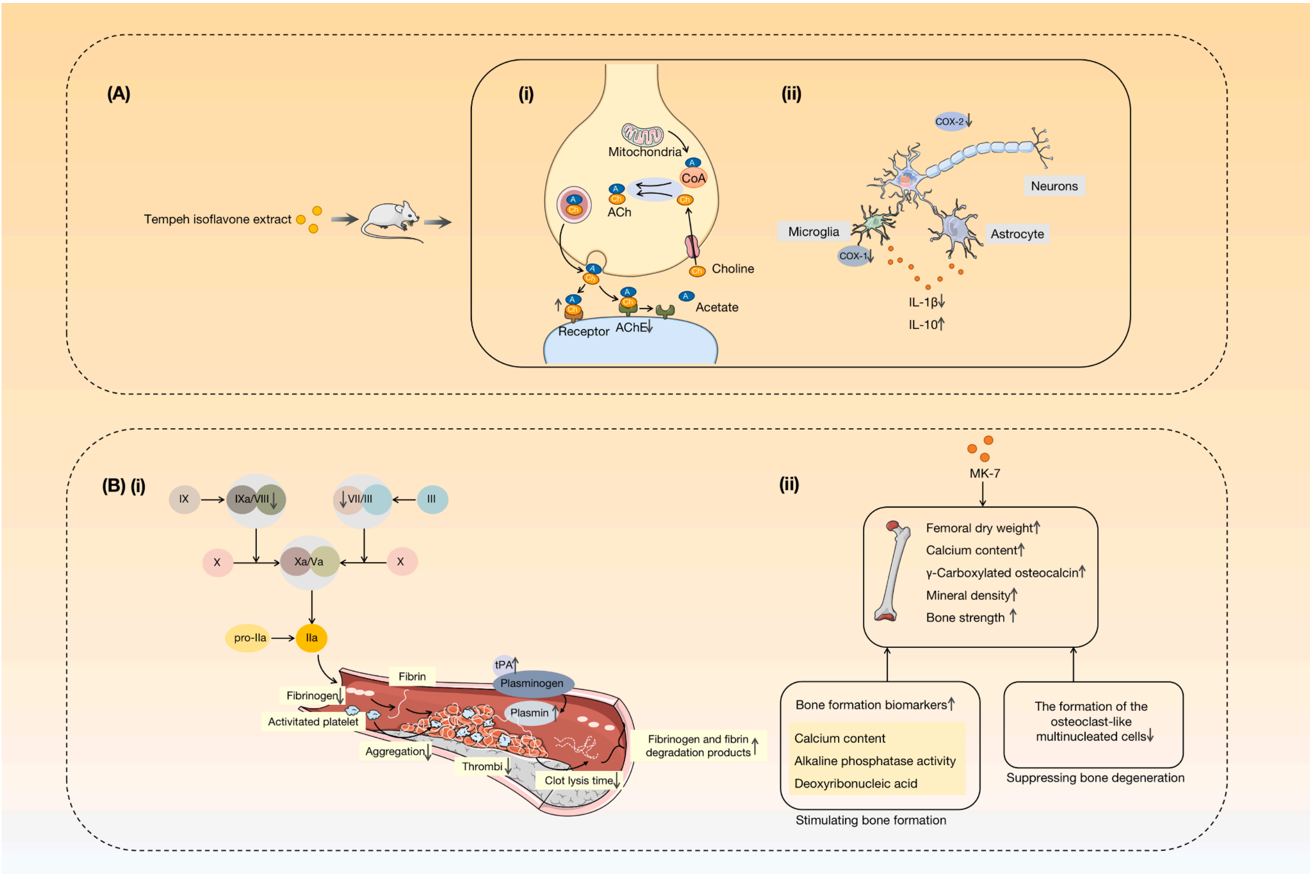

Fig. 5. **A(i)** The *tempeh* isoflavone modulated the cholinergic neuronal pathway by elevating the ACh levels through inhibiting AChE. **(ii)** Another neuroprotective mechanism of the *tempeh* isoflavone is the prevention of neuroinflammation. The *tempeh* isoflavone suppressed the activity of COX-1 and COX-2, attenuating the IL-1β levels and enhancing the IL10 levels in the Alzheimer's brain. IX, factor IX; IXa, factor IXa; VIII, factor VIII; III, factor III; X, factor X; Xa, factor Xa; Va, factor Va; pro-IIa, pro-thrombin; IIa, thrombin; tPA, tissue plasminogen activator; MK-7, menoquinone-7; AchE, acetylcholinesterase; Ach, acetylcholine. COX 1, cyclooxygenase 1; COX-2, cyclooxygenase 2. B**(i)** *Nattokinase* exhibited anti-thrombotic activity. *Nattokinase* decreased blood clotting factor (factor VII and factor VIII) activity, thereby suppressing the levels of plasma fibrinogen. Furthermore, platelet aggregation was inhibited. Additionally, the tissue plasminogen activator (t-PA) activity was elevated, increasing the plasmin activity, subsequently promoting fibrin dissolution and shortening the clot lysis time. **(ii)** MK-7 prevented the decrease in the femoral dry weight, femoral calcium content, γ-carboxylated osteocalcin concentration, mineral density and bone strength due to its dual role of stimulating bone formation and suppressing bone degeneration.

(3.15 mg/100 g) was detected in *tempeh* fermented by *R. oligosporus* and the *S. cerevisiae* group, followed by the *R. oligosporus* group (2.88 mg/100 g) and *R. oligosporus*, *S. cerevisiae* and the *Klebsiella spp*. group (1.64 mg/100 g).

5.5. Nattokinase and fibrinolytic activity

The formation of thrombi is normally caused by the gradual accumulation of fibrin and platelets. Generally, fibrin production and fibrinolysis are balanced. However, if the body is unable to degrade fibrin effectively, concerns arise regarding myocardial infarction or coagulation disorders. Therefore, fibrin degradation is pivotal to the treatment of intravascular thrombosis and cardiovascular diseases (Lippi, Franchini, & Targher, 2011). *Nattokinase*, which is secreted by *B. subtilis natto* isolated from *natto*, shows exceptionally potent fibrinolytic activity (Table 1) (Wang et al., 2009). The mature *nattokinase* peptide contains 275 amino acids and has a molecular mass of 27.7 KDa (Motaal et al., 2015). *Nattokinase* exhibits optimal activity under pH conditions ranging from 5.5 to 9.0, and the functional and structural stability of *nattokinase* are unstable under alkaline conditions. The enzyme activity is also destroyed at temperatures beyond 60 °C (Zheng et al., 2005). The resistance of *nattokinase* to high temperature and acid conditions certainly facilitated its ability to remain intact in the gastrointestinal tract. *Nattokinase* could be well absorbed in the intestine in an intact form (Ero et al., 2013).

Considerable research was undertaken to assess the thrombolytic efficacy of *nattokinase* in human/animal experiments (Fig. 5**. B (i))**. The strong thrombus lysing activity of *nattokinase* is due to its ability to degrade fibrin directly or degrade fibrin indirectly through releasing a plasminogen activator to form plasmin (Yatagai et al. 2008). In a rat experimental pulmonary thrombosis model treated with *nattokinase*, the thrombosis and plasma euglobulin lysis times were reduced, and the t-PA (plasminogen activator) level was increased. This suggested that *nattokinase* was beneficial for plasma fibrinolysis activation in vivo (Sumi et al., 2004). It has been demonstrated that *nattokinase* alleviates oxidative injury-mediated arterial thrombosis in vitro and in vivo. *Natokinase* decreased the formation of thromboxane B2 from collagen-activated platelets in a concentration-dependent manner. Oral administration of *nattokinase* for 1 week obstructed the formation of thrombosis following oxidative arterial wall injury in rats (Jang et al., 2013). *Natokinase* was proven to inhibit carrageena-induced caudal vessel thrombosis in rats. Partial thrombolysis was observed in the tail vessels of the rats treated with *nattokinase*. High levels of fibrin/fibrinogen degradation products and D-dimer were detected in rats treated with *nattokinase* (Xu et al., 2014).

Data from human trials also provided evidence that *nattokinase* has great prospects as an effective fibrinolytic agent. Forty-five subjects orally ingested capsules of *nattokinase* in an open-label, self-controlled clinical trial. The blood clotting factor (factor VII and factor VIII) and fibrinogen, which are involved in an increased risk for cardiovascular disease, were reduced. These results suggested that *nattokinase* has the potential to strengthen cardiovascular function (Hsia et al., 2009). Twelve healthy young men, who were evaluated regarding coagulation and fibrinolytic parameters, were randomized in a double-blind, placebo-controlled crossover trial, and the individuals received a single dose of *nattokinase*. Increased levels of D-dimer and fibrinogen degradation products and decreased factor VIII activity appeared hours after *nattokinase* administration. Therefore, *nattokinase* exhibits anticoagulant and fibrinolytic properties (Kurosawa et al., 2015).

Numerous studies have been devoted to optimizing the fermentation conditions of *nattokinase*. For solid-state fermentation, chickpeas were fermented with *B. amyloliquefaciens* to produce *nattokinase*. In addition, the highest yield of *nattokinase* reached 39.28 FU/g under the optimal fermentation parameters (34 °C and 50% initial moisture content) (Wei et al. 2011). Black beans, soybeans and wheat mate were used as the substrates and fermented with *B. subtilis* B060. A *nattokinase* yield of 147 U/g was obtained after fermentation (Suwanmanon & Hsieh, 2014). Liquid-state fermentation has multiple advantages over solid-state fermentation, such as simpler operation, lower cost and higher yield. The highest production (3194.25 U/ml) of *nattokinase* was achieved by *B. subtilis* after optimizing the culture medium components (glucose, peptone, $CaCl_2$, and $MgSO_4$) (Deepak et al. 2008). For *B. subtilis natto* WTC016, the optimum production of *nattokinase* was reached at 3284 IU/mL under the following conditions: 30 ℃, 7.0 pH, 2% inoculation volume, and 60 mL loading volume of liquid LB broth (Ju et al., 2019). Glutamate and metal ions are essential nutritional components for producing *nattokinase* in *B. subtilis* (Chen & Chao, 2006). Fed-batch glycerol addition is also a critical feeding strategy for *nattokinase* production (Berenjian et al. 2014).

5.6. Menaquinone-7 and bone health

Numerous epidemiological studies have been performed to assess the benefits of dietary *natto* for bone health **(**Table 1**)**. For a prefecture-level Japanese study including 74 postmenopausal women, a statistically significant inverse correlation was observed between *natto* intake and hip fracture incidence (Kaneki et al., 2001). In a cohort study including 994 women, *natto* consumption was significantly positively associated with the bone mineral density (BMD) of the hip bones and femoral necks of postmenopausal women (Ikeda et al., 2006). A cross-sectional study was carried out involving 1,662 Japanese males aged > 65 years who were living in the community. The results showed that the total hip and femoral neck BMD increased as habitual *natto* intake increased. Increases in habitual *natto* intake could reduce the risk of low BMD (Fujita et al., 2012).

The protective action of *natto* on bones is mostly mediated by vitamin K_2. Vitamin K_2 acts as a cofactor for γ-glutamyl carboxylase in the formation of carboxylated osteocalcin (Villa et al., 2016). Moreover, vitamin K_2 has the ability to induce osteoblast differentiation, regulate the mineralization of the extracellular matrix, increase the expression of bone marker genes and suppress osteoclastogenesis (Solmaz & Alireza, 2018). The most common homologs of vitamin K_2, menaquinones (MK), are MK-4 and MK-7. MK-7 possesses much superior bioavailability and a longer half-life than MK-4 (Myneni & Mezey, 2017). *B. subtilis* (*natto*) is capable of synthesizing MK-7 during the process of *natto* fermentation. MK-7 was present in *natto* at a high concentration (939 μg/100 g), which was >100-fold higher than the concentration detected in the cheese (Kamao et al., 2007).

There is much evidence in animal and human studies that MK-7 from *natto* or supplementation favors bone formation and skeletal health **(**Fig. 5**. B (ii))**. MK-7 diets elevated the MK-7 level in the serum and prevented the reduction of femoral weight and calcium loss in femoral bones in ovariectomized rats (Yamaguchi et al., 1999). Feeding *natto* and adding MK-7 improved the levels of BMD and serum γ-carboxylated osteocalcin in ovariectomized rats (Yamaguchi et al., 2000). MK-7 can stimulate femoral bone formation in 4-week-old rats in vitro. After supplementing MK-7, the alkaline phosphatase activity, DNA content, and calcium content in the diaphyseal and metaphyseal tissues in rats increased significantly (Zhu et al., 2017). Furthermore, supplementation with MK-7 entirely suppressed bone calcium loss, glucose utilization and lactate generation in the bone tissues of female rats induced by the parathyroid hormone and prostaglandin E2 (Yamaguchi, Uchiyama, & Tsukamoto, 2003). In a randomized, double-blind, placebo-controlled 3-year trial, low-dose MK-7 was administered to postmenopausal women. MK-7 administration reduced the amount of BMD lost over time in the lumbar spine and femoral neck and vertebral bone loss and improved bone strength (Knapen et al., 2013). Sixty postmenopausal women were enrolled in a double-blind, randomized placebo-controlled trial to investigate the effect of treatment with MK-7 on bone health. The carboxylated osteocalcin/undercarboxylated osteocalcin ratio was reduced remarkably for individuals without MK-7 intake (Inaba, Sato, & Yamashita, 2015).

For MK-7 solid-state fermentation, *B. subtilis natto* isolated from commercial *natto* products generated MK-7 in a medium with corn grits and soy protein. The yield of MK-7 reached as high as 67 mg/kg after optimizing the initial moisture, fermentation temperature, fermentation time, amylase and equal substrate mix (Mahanama et al., 2011). After optimizing the addition of glycerol, mannitol, yeast extract, malt extract, and $CaCl_2$ in the solid medium, the amount of MK-7 produced by B. subtilis reached 39 μg/g (Singh, Puri, & Panda, 2015). For liquid-state fermentation, MK-7 produced by B. subtilis *natto* significantly increased after optimizing the medium components, including yeast extract, soy peptone, glycerol and K_2HPO_4 (Berenjian et al. 2011). Additionally, the optimal fermentation temperature for MK-7 production generally ranges from 37 ℃ to 45 ℃ (Berenjian et al. 2015). Glycerol addition in the medium is an effective way to obtain the maximum production of MK-7 (Berenjian et al. 2012). Agitation and aeration also contributed to obtaining high concentrations of MK-7 and maximum cell density during fermentation (Berenjian et al. 2015).

5.7. Anti-cancer components

Cao et al. (2009) reported that a lipopeptide biosurfactant generated by *Bacillus natto* TK-1 decreased tumor cell viability in a dose-dependent manner. The biosurfactant induced apoptosis of K-562 and BEL-7402 cells and showed cytotoxicity against K-562 and BEL-7402 cells, with an IC_{50} of 19.1 and 30.2 mg/L, respectively (Cao et al., 2009). The cultured supernatant of *B. subtilis* in *natto* inhibited the growth of breast cancer cells, tumor vessels, and tumor tissue malignancy and decreased FOXM1 and MMP2 expression in tumor tissue (Zhang et al., 2019). Additionally, the *natto* extract showed significant antimelanoma effects in a dose-dependent manner: the extract induced oxidative stress in cancer cells and further promoted apoptosis of cancer cells by regulating the ROS reaction, cell autophagy, and cell apoptosis (Chou et al., 2021).

Seo et al. (2009) showed that *chungkukjang* fermented with *B. cereus*, *B. amyloliquefaciens*, and *B. subtilis* inhibited the proliferation of AGS gastric adenocarcinoma cells. *Chungkukjang* (1 mg/mL) had the strongest inhibitory effect (87%), and *chungkukjang* induced apoptosis and increased the Bcl-2:BAX ratio (Seo et al., 2009). Consumption of *chungkukjang* had a preventive effect against breast cancer by regulation of TGF signaling. The anticancer activity of surfactin in *chungkukjang* fermented with *B. subtilis* CSY191 increased from 2.6- to 5.1-fold when the content increased from 0.3 to 48.2 mg/kg (Lee et al., 2012). In addition, 2 mg/mL of *cheonggukjang* inhibited the growth of oral cancer TCA8113 cells by 78% by upregulating BAX, caspase-3, caspase-9, and TGF-β and downregulating antiapoptotic Bcl-2 (Zhao et al., 2013). The content of bioactive components, including proteolytic enzymes, polymeric nucleic acids, browning substances, and polyglutamic acid, is higher in *chungkukjang* compared to raw soybean (Liu et al., 2022). Trypsin inhibitors present in *chungkukjang* are believed to possess anticancer properties (Park et al., 2013).

Yuliani, Istyastono, and Riswanto (2016) reported that 0.681 % (w/w) genistein isolated from *tempeh* had cytotoxic effects on T47D breast cancer cells, with an IC_{50} of 13.174 ± 0.905 μg/mL. The water extract of *tempeh* decreased cell proliferation and induced apoptosis in human colon adenocarcinoma CaCo-2 cells (Hsu, Yu, & Chung, 2009). In addition, 3-hydroxyanthranilic acid isolated from *tempeh* showed potential as an anticancer agent and induced apoptosis of human hepatoma Huh-7 cell in a dose-dependent manner: significant cell death was observed at a concentration of > 600 μM (Matsuo et al., 1997). Compared to fermentation for 60 h (IC_{50} = 8.70 μg/mL), *tempeh* fermented for 108 h (IC_{50} = 5.20 μg/mL) showed increased inhibition of the oxidative reaction and proliferation of breast cancer MCF-7 cells (Muzdalifah et al., 2018; Athaillah et al., 2019). Oral administration of 300 mg/kg of soybean or 600 mg/kg body weight *tempeh* decreased aberrant crypt foci in the colon of DMH-treated rats by 40% (Hsu et al., 2009). Daily intake of 600 mg of *tempeh*/kg body weight decreased the number of aberrant crypt foci that were composed of more than four crypts (Hsu et al. 2009). The effectiveness of *tempeh* against cancer has been demonstrated in vitro and animal studies, but the effectiveness and the mechanism of action related to this effect in human remains largely unknown.

6. Future trends

For thousands of years, a wide variety of traditional soybean fermented foods that represent different ethnicities, cultures and societies have been developed by humans on every continent. The globalization of world food markets and rapid urbanization progress are important to the development of traditional fermented soybean products. Driven by the worldwide growing consumer demand and technological innovation, the traditional food industry has been dynamically revolutionized. The development of novel functional fermented foods is one of the foremost challenges undertaken by scientists. For several decades, fermentation-derived bioactive components and healthy functional fermented foods have attracted remarkable attention among the scientific community. Fermented soybean foods exhibit palatability, high nutritional value and health-promoting activities. However, only a few novel efficient and safe health-promoting products targeting particular consumers with diabetes mellitus or hypertension have been successfully commercialized and have entered the market. Advanced and precise technologies are required to further enhance the accuracy and efficiency of bioactive component identification in fermented foods. The effective mechanisms of action of fermented food-derived bioactive compounds need to be further mined and confirmed by combining molecular biology techniques and bioinformatics analysis tools.

CRediT authorship contribution statement

Yali Qiao: Writing – original draft. **Kenan Zhang:** Writing – review & editing. **Zongcai Zhang:** Writing – review & editing. **Chao Zhang:** Writing – review & editing. **Yan Sun:** Writing – review & editing. **Zhen Feng:** Conceptualization, Writing – review & editing, Supervision, Project administration.

Declaration of Competing 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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