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REVIEW PAPER

PRODUCTION OF ANTIOXIDANTS THROUGH LACTIC ACID FERMENTATION: CURRENT DEVELOPMENTS AND OUTLOOK

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Abstract

Antioxidants are essential in maintaining physical health as they reduce the adverse effects caused by free radical attacks. Free radicals involve in many oxidation processes in the body and may lead to malfunctions of tissues, resulting in degenerative diseases. This article comprehensively reviews the possible mechanisms of lactic acid bacteria (LAB) in increasing the antioxidant capacity of fermented foods and the mechanisms of the resulted antioxidant compound in terminating oxidation chain reactions. During food fermentation, LAB could produce antioxidant compounds, increase their bioavailability, or perform both processes simultaneously. Phenolic compounds are the primary antioxidants in plant-based foods. LAB could improve the bioavailability of phenol-based antioxidant compounds by increasing the solubility, converting isoflavone glucosides to aglycones or both. In proteinaceous foods, LAB hydrolyzes parent proteins into smaller fractions, including peptides or free amino acids. Some peptides are known as bioactive peptides owing to antioxidant activity and hence, increase the antioxidant capacity of fermented foods. Exopolysaccharides (EPS) produced by LAB also show antioxidant activity. Production of organic acids, such as lactic acid and acetic acid, change the environmental pH that influences the radical scavenging activity of some compounds. An increase in antioxidant capacities of foods through LAB fermentation supports the development of fermented foods as a part of functional foods that can provide additional health benefits beyond their basic nutritional functions.

Keywords: antioxidants, bioactive peptides, exopolysaccharide, isoflavone, lactic acid bacteria, phenolic compounds.

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Introduction

Oxidative stress leads to free radical formation, releasing compounds like reactive oxygen species (ROS) and reactive nitrogen species (RNS). Free radicals are atoms or molecules with unpaired electrons in their valency shell. These include hydroxyl radical ($OH^{\bullet}$), superoxide radical ($O_2^{\bullet-}$), and hydrogen peroxide (H_2O_2) (Fleming & Luo, 2021). They are very reactive in inducing oxidation which damages healthy cells. The sources of free radicals could be both from inside and outside of the body. The body produces typically free radicals during respiration and metabolism in small amounts. The autooxidation reactions, especially in humans generate more free radicals by the electron transport chains (Chandra & Sharma, 2020; Li *et al.*, 2013). From the outside, the most contributors of free radicals are polluted environments, such as industrial chemicals, cigarette smoking, air, and water pollutants. Additionally, the consumption of toxic products and UV radiation stimulate free radical formations (Sarmadi & Ismail, 2010).

The oxidation can occur in food systems or inside the body. In food systems, it results in the decline of food quality and safety due to the formation of free radicals, off-flavors, and toxic by-products. Oxidative stress imposes a big problem in physical health, mainly if there is an imbalance between reactive oxygen (or other radical species) production and the antioxidants (Liguori *et al.*, 2018). Free radicals involve in many destructive reactions. This leads to lipid peroxidation and oxidative damage to DNA and eventually causes cell damage and eventually tissue malfunctions. It increases the risk of various diseases, such as cardiovascular disease (CVD), carcinogenesis, atherosclerosis, inflammation, premature aging, and diabetes mellitus (Chandra & Sharma, 2020; Pan *et al*., 2020).

The body has an immune system to minimize the adverse effect of free radicals through antioxidative defenses. Antioxidants terminate oxidation reactions through several mechanisms, such as stabilizing free radicals, chelating pro-oxidant ions, or increasing antioxidant enzyme production. Naturally, the body produces antioxidants to protect cells from ROS or other free radical attacks. Cellular and extracellular fluids contain antioxidants, *e.g*., glutathione, vitamin C, and some antioxidant enzymes (*e.g.*, catalase, superoxide dismutase, peroxidase) (Chandra & Sharma, 2020). However, additional dietary antioxidant intake is important to support the defenses of the human body against free radicals. These antioxidants may be in form of nutrients (*e.g*., vitamin A, C, E, peptides) and phenolic compounds. Different antioxidants exhibit different mechanisms and scavenging activities in the prevention of oxidative reactions. Some compounds can act as an antioxidant by hydrogen atom transfer and/or single electron transfer to terminate oxidation chain reaction, and others have the ability to chelate transition metals. They can react either by a predominant mechanism or multiple mechanisms (Santos-Sánchez *et al.*, 2019). Fruits and vegetables are good sources of natural antioxidants (Chandra & Sharma, 2020). Besides naturally occurring antioxidant compounds, the activities of microorganisms during fermentation may exhibit an array of compounds which some of them can exhibit antioxidant activities (Mora-Villalobos *et al*., 2020). There has been an increased interest in microbiologically produced antioxidants because microbes are considered efficient producers of secondary metabolites whereas some demonstrate antioxidant properties (Chandra & Sharma, 2020). Many fermented foods are reported to show antioxidant activity (Hur *et al.,* 2014; Verni *et al.,* 2019).

There are several improvements mechanisms in antioxidant capacity during fermentations, through pH modification, increasing the bioavailability of antioxidant compounds, and producing antioxidative metabolites. Lactic fermentation can produce or improve the bioavailability of some antioxidants, mainly peptides, exopolysaccharides (EPS), and phenolic compounds (Hur *et al.*, 2014). In addition to direct reactions with the free radicals, LAB metabolites also induce the production of endogenous antioxidants (such as glutathione (GSH)) or antioxidant enzymes (e.g. superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), and peroxidase) (Lin *et al.*, 2018).

Fermentation is a method that can be applied to improve the quality, safety, and functionality of the products (Lee & Paik, 2017; Nuraida, 2015). This technology has been used for a long time to produce traditional foods, especially in Asia. Some popular fermented products in Asia are *natto*, *tempeh*, yoghurt, *kimchi*, and others. (Lai *et al.*, 2013). Lactic acid bacteria (LAB) are popularly involved in food fermentation and are mostly found in Asian fermented food products (Rhee *et al.,* 2011; Nuraida, 2015). LAB are Gram-positive, non-spore-forming bacteria which are either coccus or rod-shaped. These bacteria types are in the Lactobacillales order. They generally include *Lactobacillus, Lactococcus, Streptococcus, Leuconostoc,* and *Pediococcus*. Other LAB characteristics include their aerotolerant anaerobicity, DNA base composition less than 53 mol% G+C, and the absence of catalase (Florou-Paneri *et al.*, 2013). There are two types of LAB based on their carbohydrate metabolism, homofermentative and heterofermentative. Homofermentative LAB only convert carbohydrates into lactic acid. Meanwhile, heterofermentative LAB produce a mixture of compounds, such as lactic acid, acetic acid, ethanol, and carbon dioxide (Nuraida, 2015).

Fermentation using LAB is an effective way to produce beneficial metabolites for humans, including bioactive peptides (Venegas-ortega *et al.*, 2019) and vitamins (Mahara *et al.*, 2019). LAB fermentation also improves the bioavailability of minerals and phenolic compounds (Rekha & Vijayalakshmi, 2010). It can also reduce antinutrients that usually limit the nutritional benefits of food products (Sanjukta & Rai, 2016). Moreover, LAB fermentation is effective in lowering phytates and saponins (Lai *et al.*, 2013).

One of the unique health benefits of LAB fermentation includes its ability to increase the antioxidant activity of food products (Chandra & Sharma, 2020). There are several impacts of LAB fermentation on antioxidant activity. Production of organic acids, such as lactic acid and acetic acid, modify pH values. The change of the environmental pH influences the radical scavenging activity of some compounds. For example, the catechin stability of green tea is pH-dependent, where it is stable in acidic media and unstable in alkaline solutions. The ability of cell wall–degrading enzymes to release bioactive compounds is remarkably influenced by pH. The pH also determines the protonation state, a variable that the antioxidant activity of phenolic compounds depends on (Hur *et al.*, 2014). Some LAB strains can provide antioxidants by modulating the gene expression of antioxidant enzymes, such as SOD, CAT, and GSH (Noureen *et al.*, 2019). LAB have enzymes that are useful to produce or improve the bioavailability of antioxidant metabolites (Hur *et al.*, 2014).

LAB can produce several metabolites, such as exopolysaccharides (EPS) and peptides, that can scavenge free radicals (Rahbar *et al.*, 2019; Chandra & Sharma, 2020). LAB fermentation increases the antioxidant activity of milk (Sarita & Suntornsuk, 2016). Fermented soybean products showed higher antioxidant capacity than raw yellow soybeans (Xu *et al.*, 2015). Fermentation of soymilk by *Lactobacillus acidophilus* and *Lactobacillus casei* produced more superior antioxidant activity than unfermented soymilk (Ahsan *et al.*, 2020). The antioxidant activity of goat milk cheese increases during ripening using LAB culture up until 60 days of storage (Kocak *et al.*, 2020). A similar result was also shown in yoghurt fermentation, in which there were increased levels of ABTS radical scavenging activity during storage. It is related to LAB's activity, which produces small peptides during fermentation (Perna *et al.*, 2013). Fermentation of *Lactobacillus acidophilus* on milk improved the antiradical capacity of the final product. Fermentation of Tef *injera* had a better radical scavenging activity than its unfermented counterpart (Shumoy *et al.*, 2018). The fermentation of black tea was also reported to promote bioactive potential and synergism among metabolites for repressing oxidation (Villarreal-soto *et al.*, 2019).

Lactobacillus plantarum increased the antioxidant capacity of mulberry juice. The increase in the capacity was related to the phenolic profile changes after fermentation (Kwaw *et al.*, 2018). The activity of *Lactobacillus plantarum* improved the antioxidant capacity of apple juice by also modifying its phenolic composition. The apple polyphenols can inhibit the proliferation of cancer cells and attenuate LDL cholesterol oxidation. The problem is the low bioavailability of several apple polyphenols. The fermentation process by LAB resulted in higher bioavailability and increased the benefit of the compounds (Li *et al.*, 2018). Dry fermented sausages have been reported to contain a dipeptide IY (isoleucine and tyrosine) which exhibits antioxidant activity. This peptide was generated from the C terminal position of DSGDGVTHNVPIY (Gallego *et al.*, 2018). The activity of three LAB strains (e.g. *Lactobacillus farciminis* H3, *L. farciminis* A11, and *L. sanfranciscensis* 14) in dough fermentation exhibit antioxidant and anti-inflammatory activity by reducing ROS and suppressing the NF-κB pathway (Luti *et al.*, 2020). The NF-κB pathway is responsible for inducing pro-inflammatory genes. Normally, NF-κB is beneficial to activate the innate immune cells. However, deregulation of NF-κB can cause excessive and long lasting inflammatory responses and contribute to various inflammatory diseases (Liu *et al.*, 2017).

Antioxidant compounds in LAB-based fermented foods

In proteinaceous materials, LAB have the potential to produce bioactive peptides. Bioactive peptides from the digestion of protein by LAB are the main antioxidant compound in yoghurt (Sarita & Suntornsuk, 2016). In plant-based fermented products, LAB's activity on phenolic compounds provides positive effects to improve antioxidant activity in different ways, which include increasing their biological activity and solubility (Verni *et al.*, 2019). Lactic fermentations produce several types of metabolites such as EPS that pose antioxidant capacity which is dependent on the substrate and LAB strain. EPS are usually produced from foods that contain fructans or glucans (Sanalibaba & Cakmak, 2016). The previously mentioned compounds will be discussed in the following sections.

Phenolic compounds

Phenolic compounds are secondary plant metabolites that exist naturally in plant-based materials. They are considered essential substances in plants with several beneficial health effects for the human body (Muñoz *et al.*, 2017). The phenolic compounds are synthesized through the shikimic acid pathway. It usually produces amino acids like phenylalanine or tyrosine (Zeb, 2020). Phenolic compounds consist of many molecules, including phenolic acid, flavonoids, stilbenes, and lignans (Rodríguez *et al.*, 2009). Generally, phenolic compounds are categorized into two classes, simple phenols and polyphenols. Simple phenols include coumarin and phenolic acid. Polyphenols are divided into flavonoid and non-flavonoid compounds. Flavonoid compounds are flavonols, flavones, and flavononols (Jomová *et al.*, 2019). A high concentration of dietary phenolic compounds reduces the risk of several diseases, such as breast cancer, neurodegenerative diseases, and CVD (Sergazy *et al.*, 2019). Phenolic compounds have antioxidant properties with some health benefits, including anti-inflammatory, antidiabetic, and vasodilatory effects (Rodríguez *et al.*, 2009). It has also shown antiproliferative effects on tumor cells (Lai *et al.*, 2013).

LAB fermentation to improve bioavailability of phenolic compounds

Total phenolic compounds of soymilk fermented by LAB displayed significantly higher than unfermented ones. The ability of LAB to metabolize phenolic compounds receives great interest to produce a better quality of antioxidants, such as hydroxytyrosol and pyrogallol. The most frequently used LAB species in the fermentation of rich phenolic plant materials is *Lactobacillus plantarum* (Rodríguez *et al.*, 2009). Table 1 shows selected studies on the phenolic antioxidant activity of LAB-based fermented foods.

LAB improve the antioxidant capacity of phenolic compounds through several mechanisms, which include releasing them from food matrices to give better bioavailability (Verni *et al.*, 2019). The increase of antioxidant activity is because of the release of flavonoids from the plant matrices. The presence of LAB enzymes can break down starch and cell walls, facilitating the release of flavonoids. The presence of proteases, α-amylase, and other enzymes influence the antioxidant capacity of fermented foods (Hur *et al.*, 2014; Verni *et al.*, 2019). Another mechanism is by converting isoflavone glucosides or polyphenols into aglycones (Marazza *et al.*, 2012). The increased bioavailability of phenolic compounds is due to their conversion of complex phenolics into simpler forms and depolymerization reaction by phenoloxidase enzyme or LAB (Kwaw *et al.,* 2018; Hur *et al.*, 2014). The result of fermentation increases the availability of compounds donating protons thus increasing antioxidant capacity (Kwaw *et al.*, 2018). However, strain types and process conditions have to be optimized to get health-promoting phenolic compounds (Markkinen *et al.*, 2019).

Table 1. Antioxidant activity of phenolic compounds in plant-based lactic fermented foods.

LAB types	Fermented foods	Results	References
Lactobacillus plantarum 90, *Lactobacillus helveticus* 76, *Lactobacillus casei* 37, *Lactobacillus paracasei* 01, *Lactobacillus acidophilus* 85, *Bifidobacterium lactis* 80	Fermented apple juice	LAB fermentation improved DPPH radical scavenging activity and ferric reducing antioxidant power (FRAP). ABTS radical scavenging activity decreased upon fermentation	Wu *et al*., (2020)
Lactobacillus plantarum subsp. *plantarum*	Sourdough	Antioxidant activity based on the FRAP assay was significantly increased upon fermentation by Lactobacilli.	Hashemi *et al*., (2019)
Lactobacillus plantarum	Fermented wheat dough	Two strains of *L. plantarum* strains (29DAN, 98A) had significantly higher FRAP value compared to the control.	Antognoni *et al*., (2019)
Lactobacillus plantarum ATCC14917	Fermented apple juice	Antioxidant activity was increased during fermentation based on the measurement of DPPH and ABTS scavenging activity	Li *et al*., (2018)
Lactobacillus plantarum Lp-115™	Fermented mulberry juice	Fermentation increased DPPH radical scavenging activity and provided positive impact to scavenge ABTS radical and FRAP	Kwaw *et al.*, (2018)
L. plantarum C2	Fermented Myrtle berries	Fermented Myrtle berries had higher DPPH and ABTS scavenging activity than unfermented ones, and BHT added. LAB fermentation also inhibited lipid peroxidation.	Curiel *et al.*, (2015)

LAB also improves soluble phenolic compound (SPC) content in fermented products. Fermentation of Tef *injera* improved the bio-accessibility of phenolic compounds by the increase of soluble phenolic concentration. Their radical scavenging activity was also better than an unfermented control group (Shumoy *et al.*, 2018). Fermentation with LAB also changed SPC concentration in kombucha tea. It was higher compared to its unfermented counterpart. Increasing SPC concentration was the main factor of antioxidant activity enhancement (Villarreal-soto *et al.*, 2019). The increasing antioxidant activity was observed in fermented pomegranate juices as well. There were two new phenolic derivatives from catechin and α-punicalagin present in the fermented juices (Valero-cases *et al.*, 2017). *Lactobacillus plantarum* fermentation improved phenolic and flavonoid content in mulberry juice (Kwaw *et al.*, 2018). Apple juice had lower total phenolic and flavonoid content after fermentation by *Lactobacillus plantarum* ATCC14917. The metabolism of LAB converts phenolic compounds into its derivatives, including 5-*O*-caffeoylquinic acid (5-CQA), quercetin, and phloretin. The derivates had a more substantial antioxidant capacity than unfermented phenolics and flavonoids (Li *et al*., 2018).

The environmental conditions have effects on the phenolic compound metabolism by LAB. Free ellagic acid concentration did not change in fermented juices because the compound was insoluble in low pH (Valero-cases *et al.*, 2017). Interaction among phenolic compounds also influences the antioxidant capacity. The combination of gallic and protocatechuic acid with phenolic acid showed a synergistic effect and higher antioxidant activity compared to the individual compounds. Conversely, vanillic acid with major phenolic acid resulted in adverse effects and decreased antioxidant activity. The chemical structure and the number of hydroxyl groups in the phenolic compound might be responsible for determining the type of interaction. This information is vital to optimizing the formulation of functional foods (Hugo *et al.*, 2012).

There are several enzymes of LAB which can metabolize phenolic compounds. β-glucosidase hydrolyses glucoside phenols to form aglycones. The presence of glucose partially inhibited the activity of β-glucosidase. Esterase is involved in the second step of phenolic degradation and it is unaffected by glucose. *Lactobacillus plantarum* contains phenolic acid decarboxylase to decarboxylate *p*-coumaric, ferulic acid, and caffeic acid to their vinyl derivatives. The environmental stress caused by phenolic compound toxicity is considered the main factor in decarboxylase enzyme production by the LAB (Rodríguez *et al.*, 2009). Tannase or tannin acyl hydrolase is another LAB enzyme that hydrolyzes phenolic compounds. The role of tannase is to catalyze the hydrolysis reaction of ester bonds in tannin or gallic acid. Another report indicates the function of glucose as the energy source of *L. plantarum* in phenolic transformation (Li *et al.*, 2018). The pectinase treatment for pectin–containing food increased total phenolics and flavonol aglycones (Markkinen *et al*., 2019).

Conversion of isoflavone glycosides to aglycones by LAB

Isoflavones are important polyphenols in various plants, mainly in soybean and soy-based foods (Marazza *et al.*, 2012). Isoflavone synthesis starts from phenylalanine, followed by naringenin as an intermediate product. Then, naringenin is transformed into genistein by synthase and dehydratase, two necessary isoflavone enzymes, especially in soybeans. Other specific isoflavones enzymes are chalcone reductase and two types of chalcone isomerase. These enzymes, together with synthase, convert another intermediate naringenin chalcone into daidzein. The backbone of the isoflavone chemical structure is 3-phenyl chromen-4-one (Hsiao *et al.*, 2020). It is a natural metabolite of plants (Donkor & Shah, 2008) and is naturally synthesized as a defense mechanism against pathogenic bacteria or fungi through the phenylpropanoid pathway. The content of isoflavones varies in different kinds of plants and processed food. Soybean and its derivatives are the richest in isoflavones. The amount of isoflavones in soybean ranges from 1.2 – 4.2 mg/g (Hsiao *et al.*, 2020). This compound's potential health benefits include chronic disease prevention, such as CVD and cancer (Gaya *et al.*, 2017; Malashree *et al.*, 2012). The challenge is, generally, the bioavailability of isoflavones is low because of their structure. (Hsiao *et al.*, 2020). Isoflavones consist of 12 chemical constituents divided into four groups: three aglycones, three glucosides, three malonyl-glucosides, and three acetyl-glucosides. The different structures have different biological activities. Aglycones provide better bioavailability as they are free forms of isoflavones and more accessible to absorb in the small intestine than glucosides (Nuraida, 2015; Limón *et al.*, 2015; Malashree *et al.*, 2012; Yuksekdag *et al.*, 2018). The glucoside forms of isoflavones are more water-soluble and polar than the aglycones. The structure of glucosides makes it difficult for them to pass through the intestinal epithelium (Hsiao *et al.*, 2020). This is due to their more complex structure as they are conjugated with glucose, with the addition of their high molecular weight and hydrophilicity, hence the poor absorption in human bodies (Malashree *et al.*, 2012). Isoflavone glucosides will be hydrolyzed by intestinal enzymes and microbial glucosidase in small and large intestines. The mentioned process will convert the isoflavone into its aglycone form. Daidzein and genistein are hydroxylated in the liver, catalyzed by phase I enzyme (cytochrome P450, CYP) and phase II enzymes (UDP-glucuronosyltransferase, UGT), then sulfotransferase (SULT). The products of the process are the glucuronide and sulfate forms of isoflavones. These metabolites are then transported through bile and excreted into the intestinal lumen. The colonic microbiota will conduct further hydroxylation and biotransformation to produce equol (Hsiao *et al.*, 2020). Equol is an isoflavone derivative with estrogenic activity (Mustafa *et al.*, 2020).

The increase of antioxidant capacity was related to the change of isoflavone aglycone proportion. There is a rise in isoflavone aglycone content in fermented soybean products in comparison to levels in raw soybeans (Xu *et al.*, 2015). Isoflavone glycosides will be metabolized to isoflavone aglycones before getting absorbed into the bloodstream. The parameter for the biological activity of isoflavones is based on the aglycone content because of its rapid absorption and estrogenic activity (Gaya *et al.*, 2017). It was reported that human blood isoflavone levels were increased after soymilk consumption, but the increase was more rapid after lactic fermented soymilk intake (Takagi *et al.*, 2015). Soymilk fermentation hydrolyses isoflavone glucosides into aglycones. There was a noticeable reduction of isoflavone glucoside, malonylglucoside, and acetylglucoside isoflavone. In contrast, the amount of isoflavone aglycones increased significantly. Fermentation of soymilk by *Lactobacillus casei* and *L. acidophilus* in tofu production increased the aglycone to glycosylate ratio. Fermented soymilk had a higher antioxidant activity due to the rise of isoflavone aglycones (Marazza *et al.*, 2012). Elevated isoflavone aglycones improve the health benefits of soymilk (Donkor & Shah, 2008). Table 2 shows the role of fermentation in the formation of isoflavone aglycones.

Table 2. The role of soy isoflavone transformation on antioxidant activity.

LAB types	Fermented foods	Antioxidant activity	References
Lactobacillus paracasei HII02	Fermented soy broth	Antioxidant activity of fermented soybeans was slightly higher based on ABTS scavenging activity and FRAP assay.	Sirilun *et al.*, (2017)
Lactobacillus rhamnosus CRL981	Fermented soy milk	DPPH radical scavenging activity increased during fermentation. The antioxidant capacity was also improved based on measurement by β carotene bleaching and FRAP methods. Isoflavone extract from sample inhibited oxidation of DNA.	Marazza *et al.*, (2012)
Lactobacillus plantarum P1201	Fermented soy milk	There was an increased in ABTS radical scavenging activity of fermented soy milk	Lee *et al.*, (2018)
Lactobacillus plantarum HFY09	Fermented soy milk	Soy isoflavone aglycone reduced ageing symptoms and increased some antioxidants enzyme in serum, liver, and tissue. The assessment was conducted *in vivo* using mice.	Zhou *et al.*, (2021)

The isoflavone conversion is the result of β-glucosidase enzyme activity towards isoflavone glucosides (Marazza *et al.*, 2012). The increasing activity of β-glucosidase coincides with the decreased glucosides and increased isoflavone aglycones in fermented soymilk. The concentration of isoflavone aglycones has a significant and direct correlation to the enzyme activity in soymilk fermentation with *L. acidophilus*, *Bifidobacterium*, and *L. casei* (Guadamuro *et al.*, 2017). LAB produces the β-glucosidase enzyme that can break down β-glucosidic bonds responsible for conjugating the ring structure of isoflavones with the sugar moieties. This enzymatic reaction breaks down isoflavone glycosides into isoflavone aglycones and sugar molecules (Donkor & Shah, 2008). Besides the isoflavones in soybean, other plant–based isoflavonoid types can be found. As mentioned before, two major isoflavones are daidzin and genistin. Both are *O*-glycoside conjugates of daidzein and genistein. Other sources of isoflavonoids include red clover (*Trifolium pretence*) and kudzu root (*Pueraria iobata*). Red clover contains biochanin A and formononetin, which are methoxylated genistein and daidzein. Kudzu root is rich in puerarin, the *C*-glycoside of daidzein. Similar to soy isoflavones, they should be in aglycone forms to provide better biological activity than the glycosylated or methoxylated forms. On the contrary, it is more challenging to break *C*-glycoside bonds than *O*-glycoside bonds. Limitations in formononetin and biochanin A demethylation are due to the few known bacterial strains capable of their bioconversions (Gaya *et al.*, 2017).

The level of glucoside–to–aglycone transformation depends on some factors, including starter (LAB strains), β-glucosidase enzyme activity, and fermentation conditions (Malashree *et al.*, 2012). The LAB strains and compositions determine the final result of fermentation, including in the isoflavone conversion level (Takagi *et al.*, 2015). The activities of bifidobacteria deglycosylated glycosides had wide variations between strains and species. Substrate specificity and the number of β-glucosidase encoding genes account for the different transformation levels among LAB species and strains (Guadamuro *et al.*, 2017). LAB compositions during fermentation also influence the bioconversion of isoflavone glucosides (Takagi *et al.*, 2015). A mixed culture between *S. thermophilus* and *Lactobacillus helveticus* reduces the ability of the *L. helveticus* to transform soy isoflavones (Champagne *et al.*, 2010). Substrates also influence isoflavone glucoside conversions. The content of isoflavone aglycones was reported lower in fermented soymilk with added sucrose than fermented soymilk without sucrose (Wei *et al.*, 2007).

Mechanism of action of phenolic compounds as antioxidant

Phenolic compounds have several antioxidative mechanisms because of their ideal chemical structure in exhibiting antioxidant activity. It is proposed that isoflavone antioxidants work by direct reactions with reactive oxygen species and other oxidants (Ziaei & Halaby, 2017). The number of hydroxyl groups and antioxidant capacity are directly proportional. Flavonoids have more hydroxyl groups than phenolic acids. It results in higher antioxidant activity than the latter (Zeb, 2020). The hydroxyl group facilitates hydrogen or electron donation, which scavenges free radicals or chelates metal ions. It terminates the generation of new radicals (Verni *et al.*, 2019). The benzene ring in phenols provides benefits in electron interactions. The mentioned structures stabilize themselves by delocalization. Stabilization of free radicals by phenolic compounds could be by hydrogen atom transfer (HAT), single electron transfer (SET), sequential proton loss electron transfer (SPLET), or transition metal chelation (TMC). In the mechanism of HAT, phenolic antioxidants provide H-atoms to stabilize free radicals, resulting in non-radical substances such as RH, ROH, and ROOH. Hydrogen donation can occur when the antioxidant has a lower reduction potential than free radical species. Phenolic antioxidants can also act by the SET mechanism, where the benzene ring transfers the electron to form a radical anion, which is a more stable or less reactive radical. The aromatic ring of phenolics stabilizes itself by distributing the electron over the whole molecule. SET can occur if the ionization potentials between antioxidant and radical are low. In SPLET, the antioxidant releases a proton to the free radical to form an anion radical, followed by electron donation, resulting in a stable molecule (Zeb, 2020). As for its metal ion chelator property, phenolics can maintain their catalytic activity and reduce metals to minimize the metal's pro-oxidative ability. The hydrophobic properties of benzenoid rings and their hydrogen-bonding ability make phenolic compounds interact strongly with protein. By those characteristics, phenolic compounds can bind radical–producing enzymes, including cytochrome P450, lipoxygenase, xanthine oxidase, and cyclooxygenase (Pereira *et al.*, 2009). Apoptosis is another possible mechanism of the inhibition effects. Genistein can initiate apoptosis to program the death of cancer cells and prevent further damage. The other proposed mechanisms are estrogen agonists, inhibitors of tyrosine kinases metastasis, and topoisomerase inhibitors (Barnes, 2010).

Bioactive peptides as antioxidants

A peptide is a short chain of amino acids that may have bioactivities after getting released from the parent protein. There are several methods to produce peptides, such as chemical hydrolysis, enzymatic hydrolysis, and fermentation (Sitanggang *et al*., 2021; Tadesse & Emire, 2020). The proteolytic activity of LAB breaks down large proteins into peptides that may have bioactive properties (Xiang *et al.*, 2019). Fermentation is a cost-effective method to produce peptides. It is economically feasible and more environmentally friendly for large-scale productions (Tadesse & Emire, 2020). Protein hydrolysis by LAB during fermentation produces a large number of peptides (Pan *et al.*, 2020). Bioactive peptides usually contain 2 – 20 amino acids with various molecular weights (Sitanggang *et al.*, 2020). Bioactive peptides must maintain their structure to provide their biological activity to the targeted tissue or cell. Morsels of peptides can escape by intestinal hydrolysis and are absorbed in the active form (Sarmadi & Ismail, 2010). Several bioactive peptides from LAB activities provide health benefits, such as antimicrobial, metal-binding, antioxidant, immunomodulatory, cell cycle and apoptosis modulating, antithrombotic, antihypertensive, and cholesterol-lowering effects (Pessione & Cirrincione, 2016; Sanjukta & Rai, 2016).

Some bioactive peptides from fermentation were reported to have antioxidant capacities (Sanjukta & Rai, 2016) and showed peroxidation inhibition (Tonolo *et al.*, 2020). Peptides can prevent membrane peroxidation, inhibiting protein and nucleic acid damage, thus improving SOD and GSH-Px activity (Pan *et al.*, 2020). The proteolytic activity of *Lactobacillus fermentum* in goat milk was reported to generate antioxidant peptides. They achieved maximum proteolytic activity at 48 h at 37^{o}C incubation (Panchal *et al.*, 2020). The peptide fractions from goat milk yoghurt showed antioxidant activity. They were released during fermentation and contained fragments from casein (Farvin *et al.*, 2010). The usage of mixed culture of LAB for white brined goat milk cheese also demonstrated antioxidant activity. Multiple peptides were produced during fermentation contributed to the enhancement of

DPPH scavenging ability (Kocak *et al.*, 2020). Aside from animal products, lactic fermentation also exhibited peptides in plant-based materials. Fermentation of soymilk by *L. plantarum* produced peptides with antioxidant activity. Based on its LC-MS/MS characterization, the fermentation released 17 soy peptides with antioxidant activities (Singh & Vij, 2017). Soymilk fermented by *L. plantarum* HFY09 provided anti-aging effects in mice. During the fermentation, *L. plantarum* HFY09 hydrolyzed protein into small peptides and transformed glucoside isoflavone into aglycone forms. Both may be related to the activation of the Nrf2 signaling pathway and increase the total amounts of superoxide dismutase (T-SOD), glutathione peroxide (GSH-Px), glutathione (GSH), and catalase (CAT) in serum (Zhou *et al.*, 2021). Aglycone isoflavone could be metabolized into equol, which will stimulate the accumulation of nitric oxide synthase (eNOS) in endothelial cells, producing nitric oxide (NO). In the presence of NO, Nrf2 will translocate to the nucleus and facilitate transcription of antioxidant enzyme (Zhang *et al.*, 2013). However, several bioactive peptides can activate Nrf2 by allowing the translocation of Nrf2 from the cytosol to the nucleus (Tonolo *et al*., 2020). Table 3 shows the antioxidant activity of peptides in lactic fermented foods.

Table 3. Antioxidant activity of peptide in lactic fermented foods.

LAB types	Fermented foods	Antioxidant activity	Identified peptides	References
Lactobacillus plantarum HFY09	Fermented milk	Increased levels of antioxidant enzymes in serum, liver, and brain (animal *in vivo*); and reduced ageing symptoms	Small peptides	Zhou *et al.*, (2021)
Lactobacillus casei, Lactobacillus plantarum, Lactobacillus bulgaricus	Goat milk cheese	Antioxidant activities increased until day 60 based on DPPH and ABTS assay	Hydrophobic peptides	Kocak *et al.*, (2020)
actobacillus fermentum	Fermented goat milk	The highest antioxidant activity was achieved after 48 hours of the incubation period, based on ABTS, Hydroxyl free radical, and superoxide free radical scavenging activity	YIPIQYVLSR, HPHPHL SFMAIPPK (10 – 15 kDa); IAKYIPIQYVLSR (10 kDa), SAEEQLHSMK (3 kDa)	Panchal *et al.,* (2020)
		The highest antioxidant activity was achieved after 48 hours of the incubation periods.		

LAB types	Fermented foods	Antioxidant activity	Identified peptides	References
		The highest antioxidant activity was achieved after 48 hours of incubation		
Lactobacillus rhamnosus BD2 and *L. kefiri* YK4	Fermented milk	>10 kDa peptide fractions had higher DPPH radical scavenging activity than <3 kDa fractions	FPPQSV and YQEPVLGP VRGPFPIIV	Yusuf *et al.*, (2020)
Streptococcus thermophilus, Lactobacillus delbrueckii subsp. *Bulgaricus, Lactobacillus acidophilus* LAFTI® L10.	Yoghurt	DPPH radical scavenging activity was increased until the 14^{th} day, then decreased	not identified	Tavakoli *et al.*, (2019)
Lactobacillus rhamnosus	Cheddar cheese	DPPH scavenging activity and FRAP of LAB added cheese were higher than control cheese.	not identified	Liu *et al.*, (2018)
Lactobacillus rhamnosus PTCC 1637	Fermented camel milk	Fermentation increased the ABTS radical scavenging activity.	5 – 10 kDa fraction of peptide showed the highest activity	Moslehishad *et al.*, (2013)
Lactobacillus delbrueckii ssp. *Bulgaricus, Streptococcus thermophilus*	Yoghurt	Storage increased the antioxidant activities based on the measurement by ABTS assay	not identified	Perna *et al.*, (2013)
Mix strains of LAB (Lactobacillus alimentarius 15 M, *Lactobacillus brevis* 14G, *Lactobacillus sanfranciscensis* 7A, *Lactobacillus hilgardii* 51B,	Sourdough	The fermented dough had higher DPPH scavenging and lipid inhibitory activity than acidified dough	The molecular weight of antioxidant peptide <10 kDa	Coda *et al.*, (2012)

LAB types	Fermented foods	Antioxidant activity	Identified peptides	References
and *L. sanfranciscensis*				
Lactobacillus plantarum strain C2	Fermented soy milk	10 kDa fraction peptide exhibited the highest antioxidant activity based on the DPPH assay	E.SYFVDAQP KKKEEGN.K, K.SQSESYFV DAQPQQKEE GN.K, Y.FVDA QPQQKEEGN. K, N.LIKSQS ESYFVDAQP QQKEEGN.K, Q.SESYFVDA QPQQKEEGN. K, E.SYFVDA QPQQKEEGN. K, S.LKVRED ENNPFYFRSS N.S, etc.	Singh & Vij (2017)

There are many antioxidative peptides that have been identified in fermented foods, including VPYPQ-, KAVPYPQ- and KVLPVPE-casein derived peptides (Farvin *et al.*, 2010), FPPQSV-, YQEPVLGVR- and IQY-casein derived peptides (Yusuf *et al.*, 2020); and HPVPPKKK-putative cyclin derived peptide (Coda *et al.*, 2012). Identification of peptide sequences was made by using some methods, like Mass Spectrometry (MS), Edman degradation, or Enzyme-linked immunoassay (ELISA). The last two methods are quite complex because they require fractionation before sequence identification. It will be immensely tedious to apply if the hydrolysates contain hundreds of peptides. Combining biochemical and bioinformatic techniques makes the identification of peptides easier (Nongonierma & Fitzgerald, 2017).

Inside the body, peptides can be absorbed through several possible mechanisms. Their transport routes are influenced by molecular size and structure. Small peptides containing 2 – 6 amino acids are absorbed easily than larger ones. Large, water-soluble peptides are transported through paracellular transport. They will passively diffuse between cells through tight junctions. Hydrophobic peptides are transported by passive diffusion through transcellular transport. Hydrolysis-resistant small peptides are transferred via transporters in the intestinal basolateral membrane. Another transportation method for large polar peptides is binding to the cell and absorbed via vesiculation (endocytosis). The lymphatic system transports highly lipophilic peptides (Sarmadi & Ismail, 2010).

Production of bioactive peptides by LAB

LAB have specific mechanisms to improve the bioactivity of proteins. The LAB fermentation may facilitate the production of bioactive peptides through the hydrolysis of the existing parent proteins in the fermentation medium. The formation of low molecular weight peptides in fermented milk could be due to the presence of proteinases and peptidases. Cell wall-bound proteinases (PrtP family) are directly involved in the generation of peptides. Those enzymes can be found in *L. lactis, L. bulgaricus, L. casei, L. acidophilus, S. thermopilus,* and *L. casei* (Venegas-ortega *et al.*, 2019). The Proteolytic systems of LAB are efficacious in releasing bioactive peptides by degrading food proteins into smaller sequences (Pessione & Cirrincione, 2016). The utilization of casein by LAB is done through three main steps. Firstly, Cell Envelope Proteinase (CEP) degrades the protein into oligopeptides. Secondly, the peptides are taken up by cells by the action of Opp (Oligopeptide permease) or other specific peptide transport systems. Finally, oligopeptides are degraded into smaller peptides by peptidase (Hafeez *et al.,* 2014). CEP starts the proteolytic activity by hydrolyzing proteins to peptides; in this step, peptides contain 4 to 30 amino acids and released are released in extracellular media. The extracellular peptides then are transported into the cytoplasm through some transporters, including oligopeptide permease (OPP), ion-linked transporter (DtpT), and the ABC transporter. DtpT facilitates di- and tripeptides transportation through the cell wall whereas Dpp is responsible for peptides having 2 – 9 amino acid residues. In the cytoplasm, the transported peptides are cleaved by peptidases into free amino acids. Several peptidases are involved in peptide degradation, including aminopeptidases (PepN, PepC, PepS, PepA, and PepL), endopeptidases (PepO, PepF, PepE, and PepG), proline-specific peptidases (PepQ, PepI, PepR, PepX, and PepP), dipeptidases (PepD and PepV), and tripeptidases (PepT). Different LAB have shown different proteolytic activities. In addition to this, as the substrates, parent proteins may also vary in their characteristics which are associated with the actions of LAB proteases. Hence, the bioactive peptides produced through LAB fermentation are diverse in terms of amino acid residues and bioactivities (Raveschot *et al.*, 2018).

Mechanism of action of antioxidant peptides

The function of each peptide may be different due to their constituent amino acids' composition and sequence. Their amino acid side chains perform the radical scavenging capacity of peptides. Some amino acids, such as tryptophan, histidine, phenylalanine, methionine, and leucine, were reported as functional components of antioxidant peptides. The sequence and composition of amino acids determine the antioxidant capacity and the inhibitory mechanism of antioxidative peptides (Sanjukta & Rai, 2016). Aromatic amino acid residues have radical scavenging activity. Amino acids with sulfhydryl (-SH) groups, such as cysteine, also show the ability to directly interact with radicals (Sarmadi & Ismail, 2010). Peptides with Ala or Leu at the N or C terminus also show antioxidative activity (Coda *et al.*, 2012). The antioxidant activity of peptides is not only influenced by the polypeptide concentration but also their molecular weight. Different peptide sizes have different antioxidant properties (Liu *et al*., 2018).

Peptides with histidine residues were reported to have higher antioxidant activity than histidine itself. The reason is hydrophobicity. Due to the increased hydrophobicity, the histidine - peptides have better interaction with fatty acid (Farvin *et al.*, 2010). Peptides with high proportions of hydrophobic amino acids tend to have more potent antioxidative properties. (Pan *et al.*, 2020) Hydrophobic amino acid residues, including Val and Leu in peptides, provide antioxidant properties by enhancing the solubility of peptides in lipids. They enhance interactions with hydrophobic radical substances (Sarmadi & Ismail, 2010). Peptide hydrophobicity also determines the facileness in interacting with bodily organs. Hydrophobicity is directly correlated to the level of ease of antioxidant effect provision (Pan *et al.*, 2020). Some peptides also showed the synergic effect. Single peptides can exhibit antioxidant activity, and the same goes for multiple peptides (Coda *et al.*, 2012).

The antioxidant activity of peptides involves either hydrogen atom transfer, single electron transfer, or both. Tyrosine in peptides tends to transfer hydrogen atoms to stabilize free radicals. Peptides with aromatic amino acids (Tyr, His, Trp, and Phe) exhibit their antioxidative effect by donating electrons to neutralize free radicals. Cysteine, tryptophan, and histidine-containing peptides mainly function through single electron transfer. Some peptides have been reported to have metal ion chelating activity (Esfandi *et al.*, 2019). The reducing power measures the capacity to chelate metal ions based on the ability to reduce Fe^{3+} to Fe^{2+}. High levels of charged peptides from the presence of basic/acidic amino acids or phosphorylated serine residue contribute to the metal ion chelation. High-affinity antioxidants are presented when the *C*-terminal residues are constituted of acidic amino acids bound to two carboxylic acids, which have a strong metal ion chelating capacity (Farvin *et al.*, 2010). His at the *C* – terminus effectively scavenges various free radicals. Still, at N terminus, His acts as a metal ion chelator (Coda *et al.*, 2012), the metal chelation of His is related to its imidazole group (Pan *et al.*, 2020).

Bioactive peptides also may reduce oxidative stress through the Keap1-Nrf2 signaling pathway. The Nuclear factor erythroid 2-related factor 2 (Nrf2) acts as a transcription factor that plays an essential role in regulating cellular redox and endogenous antioxidant enzymes and phase II immune responses in mammals. There was a correlation between *L. plantarum* with Nrf2 and the production of antioxidant enzymes (Lin *et al.*, 2018). The Nrf2 signaling pathway is the strongest antioxidant defense system, and peptides were reported to be able to activate it. Nrf2 is inactive under normal conditions and is usually activated under oxidative stress. Activated Nrf2 will move from the cytoplasm to the nucleus (Zhou *et al.*, 2021). The interaction of the bioactive peptides with Keap1-Nrf2 promotes antioxidant enzyme production. Antioxidant peptides activate the Keap1-Nrf2 by translocating the Nrf2 transcription factor, which modulates the output of thioredoxin 1(Trx1), thioredoxin reductase 1 (TrxR1), superoxide dismutase (SOD), glutathione reductase (GR), and NAD(P)H quinone dehydrogenase 1 (NQO1), all of which are antioxidant enzymes (Tonolo *et al.*, 2020).

Exopolysaccharides (EPS)

EPS are a type of polysaccharide composed of sugar units such as glucose, fructose, mannose, galactose, rhamnose, arabinose, and xylose or other sugar derivatives, including N-acetylgalactosamine and N-acetylglucosamine. EPS are long-chained, high molecular, and water-soluble polymers. There are two types of EPS, i.e., homopolysaccharide (HoPS) and heteropolysaccharide (HePS). HoPS contain one kind of monosaccharide, whereas HePS comprises three or more categories (Sanalibaba & Cakmak, 2016). The most frequently found HoPS have glucans or fructans. HePS is primarily composed of glucose, galactose, and rhamnose. Several HePS also contain phosphate, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine, or other moieties in their chemical structure. The molecular weight of HoPS ranges from 10^5 to 10^6 Da, and HePS between 10^4 and 10^6 Da (Caggianiello *et al.*, 2016). EPS has been used widely in food production for several purposes like thickening agents, stabilizers, and emulsifying agents. EPS influences the food's rheological properties, such as texture and mouthfeel. In addition to its rheological properties, EPS also offers health benefits (Nguyen *et al.*, 2020).

Since LAB are good producers of EPS, there have been increasing interests in EPS produced by LAB for medical, chemical, and food industry applications. Some EPS can act as prebiotics that supports probiotic growth (Caggianiello *et al.*, 2016). EPS from LAB were also involved in the reduction process of cholesterol and deconjugation of glychocolate (Avci *et al.*, 2020). Several LAB also demonstrated the ability to produce EPS, which exhibit antioxidative properties (Chandra & Sharma, 2020). EPS can quench free radicals and chelate metal ions (Rahbar *et al.*, 2019; Bomfim *et al.*, 2020). *Lactobacillus plantarum* CNPC003 produced EPS, and it showed potential antioxidant capacity, especially EPS FOS (fructooligosaccharides) (Bomfim *et al.*, 2020). *Lactobacillus delbrueckii* ssp. *bulgaricus* SRFM-1 generated EPS in milk (Tang *et al.*, 2020). EPS isolated from fermented milk also showed antioxidant properties (Almalki, 2019). Wild type *L. delbrueckii* also generated strong DPPH scavenging activity, total antioxidant activity, H_2O_2 scavenging activity, and ferric reducing antioxidant power (FRAP) (Adebayo-Tayo and Fashogbon, 2020). The EPS produced by *L. plantarum* isolated from kefir showed strong antioxidant activity. EPS effectively reduced oxidative stress in aging mice, and it was shown by increasing levels of GSH-Px, SOD, CAT, and total antioxidant capacity (T-AOC) but decreased malondialdehyde (MDA) (Zhang *et al.*, 2017). EPS from *L. plantarum* LP6 inhibited lipid peroxidation and protected cells from oxidative damage (Li *et al.*, 2013). The EPS from LAB fermentation were also reported to have anticarcinogenic potentials. Some proposed anticancer mechanisms include antiproliferation, mutagenicity inhibition, apoptosis induction (Wu *et al*., 2021). The anticarcinogenic effects of EPS depend on the origin of LAB, its chemical structure, and purity (Wu *et al.*, 2021). The antioxidant activity of EPS in fermented food can be analyzed by separating them from other compounds. The sample can be mixed with trichloroacetic acid (TCA) to precipitate enzymes and protein, followed by centrifugation. The supernatant was then mixed with ethanol and centrifuge to separate the EPS. The pellets were then dissolved in deionized distilled water and dialyzed. The antioxidant capacity of EPS can be measured by DPPH, ABTS, or other methods (Almalki, 2019; Lobo *et al.*, 2019; Ayyash *et al.*, 2020). Besides using TCA, protein separation from EPS can also be done with Sevag reagent (chloroform and n-butanol), which also requires centrifugation (Li *et al.*, 2013).

Synthesis of EPS by LAB

HoPS synthesis is more straightforward than HePS. HoPS biosynthesis involves glucansucrase or fructansucrase and an extracellular sugar (sucrose for glucans synthesis, or fructose-containing oligosaccharide for fructans synthesis). In HoPS synthesis, no active transport is present in the synthetic pathway, hence also no energy expenditure; but it still requires extracellular enzyme synthesis. Monosaccharides are assembled outside of the cell (Sanalibaba & Cakmak, 2016). HePS biosynthesis, on the other hand, is a complex mechanism; it involves many enzymes and regulatory proteins. In principle, there are three main steps of HePS biosynthesis by LAB. First of all, is the production of sugar nucleotides, several genes are involved to convert them. The second step is the synthesis of repeating sugar units; sugar nucleotides from the first step are attached to the cytoplasmic membrane of the cell, then it is followed by the next nucleotide to form repeating units. The EPS-encoding gene clusters are involved in catalyzing EPS synthesis; the repeating EPS units from LAB usually contain 3 – 8 types of monosaccharides. Thirdly, the polymerization of sugar units or their derivatives to form EPS. Finally, EPS is excreted to outside cells (Nguyen *et al.*, 2020). Sugar units are synthesized in the cytoplasm; they are assembled through the formation of monosaccharides from sugar nucleotides by specific glycosyltransferases on the undecaprenyl phosphate (UDP), a lipid carrier molecule. GTF attaches the sugar nucleotide to C55-polyprenyl phosphate. Lipid-bound repeating units are moved by Wzx (flippase) from the cytoplasm, out the cell membrane, then polymerized by Wzy. The eps/cps gene clusters are responsible for encoding the enzyme and regulating EPS production from the synthesis, polymerization, and secretion (Ryan *et al.*, 2015; Caggianiello *et al.*, 2016). The type of EPS produced by LAB is influenced by the bacteria strain, nutrient, culture, and process condition. It can vary in constituents, charge, structure, linkage, and repeated side chains (Chandra & Sharma, 2020).

Mechanism of action of EPS as antioxidant

Several factors that influence the antioxidative properties of exopolysaccharides include polysaccharide conjugates, polysaccharide chelating metals, metal ion-enriched polysaccharides, and the polysaccharides' structural features. In polysaccharide conjugates, EPS can associate with other components. For example, it can conjugate with amino acids or phenolic compounds. EPS with specific functional groups, including -OH, -SH, -COOH, -PO3H3, -C=O, -NR2, -S-, and -O, can chelate metal ions. The antioxidant activity may also be exhibited by the EPS structure. EPS with low molecular weights were known to have more reducing hydroxyl group terminal to stabilize free radicals (Wang *et al.*, 2016). The chemical structure of EPS, which contains hydroxyl groups, carbon-free radicals, and sulfated groups, exhibits antioxidant activity (Wu *et al.*, 2021). A possible antioxidative mechanism is the electron donor system, where EPS transfers the electrons to terminate the oxidation reaction (Bomfim *et al.*, 2020). DPPH free radicals accept electrons or hydrogen from EPS to stabilize their molecules. EPS are also good scavengers for hydroxyl radicals and superoxide radicals (Tang *et al.*, 2020). EPS might also have chelating abilities to reduce free radical formations (Liu *et al.*, 2010;

Li *et al.*, 2014). Higher charged EPS can reduce steric hindrance and increase intramolecular repulsive force. Free radicals can be scavenged more easily in this condition (Li *et al*., 2013). EPS were also reported to have a significant role in minimizing cancer attack risks. EPS can influence the regulation of cancer-related inflammation by interrupting interactions between cancer cells and immune cells. It inhibits JAK/STAT2, NF-κb, HIF pathways (in tumor cells), and NF-κβ, p38/MAPK (in immune cells). These treatments increase anti-inflammatory cytokines (IL10) and reduce pro-inflammatory cytokines and pro-inflammatory enzymes (Wu *et al.*, 2021).

Outlook

Noncommunicable diseases (NCDs) are still being a problem in the world. CVD , cancer, diabetes mellitus, and chronic respiratory diseases were reported to account for 71% of all deaths globally (WHO, 2019). Several factors contribute to the increased risk of NCDs, including tobacco, alcohol consumption, unhealthy diet, and lack of physical exercise. Consumption of a healthy diet through balanced nutrition is essential to reduce the risk of NCD (WHO, 2019). A healthy diet is important to prevent NCD. Fruits, nuts, and vegetables are part of the diet containing high antioxidants to help reduce the negative effect of free radicals (Wichansawakun and Buttar, 2018). Plant-based diets play an important role in minimizing the risk of cancer, CVD, and other chronic diseases. The challenge of an antioxidant diet is its bioavailability. There are several factors that affect the bioavailability of antioxidants, including enzyme degradation and environmental conditions, such as temperature, pH, and light (Fleming & Luo, 2021). The other important factors are the chemical, structure of the compounds, food matrix, the concentration of the compound in the foods, the presence of anti-nutrition substances or interaction with other compounds, and others (Porrini & Riso, 2008). Improvement of bioavailability is important to enhance the health benefits of antioxidants (Abourashed, 2013). The fermentation process can improve the antioxidant activity of food products, as previously discussed. The application of fermentation technology is visible in the food industry, and it is already used worldwide. There are numerous fermented foods in the market, both animal-based food and plant-based food, which are familiar and well-accepted by consumers. Besides improving antioxidant capacity and health benefits, fermentation is also able to provide other advantages, such as extending shelf life, improving organoleptic quality, and degrading anti-nutrition substances (Sharma *et al.*, 2020).

Delivering antioxidants through diet is in line with the functional foods trend. Market demand for functional food is growing steadily because of increasing NCD prevalence and technological advancement (Tadesse & Emire, 2020). Functional food is defined as food that can provide additional benefits for health, beyond its basic nutritional functions. Functional foods are designed through several methods, including by enhancement of bioactive compounds through food processing, such as fermentation. The recent trend shows the development of fermented foods as functional food.

Conclusions

Oxidation processes cause many health problems due to free radical formations. Free radicals attack healthy cells and increase the risk of degenerative diseases. Intake of dietary antioxidants may prevent the negative effect of free radicals. Lactic fermented food consumption could contribute to the enhancement of antioxidant levels. LAB fermented foods contain antioxidants which are helpful to maintain body health. LAB fermentation can produce or improve the bioavailability of the antioxidant. LAB metabolize substrates and produce metabolites beneficial for human health. Lactic fermentation also influences the antioxidant capacity of foods by modifying environmental conditions. Lactic acid reduces pH and affects antioxidant stability.

The activity of β-glucosidase and other enzymes improve the bioavailability of phenolic compounds by increasing their solubility and converting the complex structures into their aglycone forms. The biological activity of isoflavone aglycones is higher than their glucoside counterparts. Lactic fermentation also hydrolyzes proteins into peptides. The proteolytic activity of LAB significantly contributes to the production of antioxidant peptides in fermented foods. In addition, lactic acid bacteria also can assemble monosaccharides from fructans or glucans to form EPS. Some of the EPS were identified as antioxidant compounds. The bioactive compounds present in fermented food act as an antioxidant in several mechanisms. The first mechanism is stabilizing free radicals by electron donor and/or hydrogen transfer. The second mechanism is by chelating metal ions, which can prevent metal ion-catalyzed oxidative reactions. The third mechanism is increasing the number of antioxidant enzymes such as SOD, GSH-px, and CAT. Another mechanism through interaction with the Keap1-Nrf2 signaling pathway, responsible for the production of various antioxidant enzymes.

Lactic fermentation could be used as a method to develop functional foods. Fermentation technology is already applied worldwide in food industries, and it is well accepted by consumers. High antioxidant fermented foods could be helpful against noncommunicable diseases, such as cancer, CVD, and diabetes mellitus.

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