29 Emerging Roles of Nutraceuticals from Selected Fermented Foods in Lifestyle-Related Disease Prevention

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29.1 Introduction

In the present world, lifestyle-related diseases are a major public health problem. People are prone to suffer with this type of diseases depending on their daily lifestyle behavior. Intake of high- or low-fiber diet, smoking, alcohol consumption, and physical inactivity are the major factors responsible for the occurrence of diseases like diabetes, cancer, cardiovascular diseases, and neurodegeneration diseases. Lifestyle diseases not only reduced people's quality of life and life expectancy but also create a burden on health systems and economics, and on society. In 2013, 382 million people were diagnosed to have diabetes around the world and this incidence is expected to be 592 million by 2035 (Guariguata et al. 2014; Prabu et al. 2012).

Over the last two decades, the food industry has advanced and started sophisticated research in the development of healthier, more physiological benefits, which may reduce chronic disease risk. Thus, foods are often titled as "functional"

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S. Sen, R. Chakraborty (eds.), *Herbal Medicine in India*,
https://doi.org/10.1007/978-981-13-7248-3_29

when they have nutritional components vital for healthy living or "nutraceuticals" when considered to ameliorate or prevent disease or disorders through a variety of mode of actions (Perez-Gregorio and Simal-Gandara 2017). Generally, nutraceuticals are food or part of food which play an important role in modifying and maintaining normal physiological function and help in eliminating numerous lifestyle-related diseases like obesity, cardiovascular diseases, cancer, osteoporosis, arthritis, inflammation, and nonalcoholic fatty liver diseases (NAFLD) (Ramaa et al. 2006; Prabu et al. 2012; Khan et al. 2011). Although limited clinical studies on fermented foods have been done, there is confirmation that fermented foods deliver health benefits over the starting food materials. Study revealed that high nutraceuticals containing fermented foods provide many health benefits by acting as antioxidant as well as antimicrobial and anti-inflammatory agents (Selhub et al. 2014). Thus, this chapter will elucidate the relevance, and potentially the necessity, of certain fermented foods in the human diet and describes their health benefits especially in lifestyle-related disease prevention.

29.2 Nutraceuticals and Fermented Foods

The nutraceutical industries have primarily been categorized into three major parts, notably herbal products, dietary supplements, and functional foods. Among these, herbal/natural products and the dietary supplements are fast growing. The top most countries having nutraceutical markets include the United States, the United Kingdom, and Japan (Das et al. 2012). It is estimated that demand for nutraceutical ingredients has increased 5.8% annually and in 2010, the total nutraceutical market was found to be $ 15.5 billion globally (Prabu et al. 2012). On the other hand, China and India are the fastest growing nutraceutical markets (Prabu et al. 2012). The food components used as nutraceuticals are all natural and can be classified as dietary fiber, prebiotics, probiotics, vitamins, polyunsaturated fatty acids, polyphenols, and spices (Das et al. 2012).

In the fermentation process, functional microorganisms enzymatically transform the chemical constituents of raw materials of foods thereby enhancing the bioavailability of nutrients, enriching tastes and smells of the food, making the biopreservative process, removing toxic components, and finally producing antioxidant, antimicrobial, and probiotic functions with stimulating health-promoting bioactive compounds (Marco et al. 2017; Tamang et al. 2009). Nutraceuticals, for example, phenolic compounds in foods, have attracted great interest due to their beneficial effects on human health. Fermentation process can modulate phenolic compounds content in different foods. *Lactobacillus*-mediated fermented mottled cowpea had the highest soluble total phenolic content (TPC) (about 750 mg GAE/100 g DW) among the edible legumes compared to nonfermented samples (Gan et al. 2016). Soybeans incubated with *Aspergillus oryzae* at 30 °C for 48 h resulted in 23 times elevated genistein aglycones content when compared to unfermented soybean flour (da Silva et al. 2011). Barley fermented by *Lactobacillus johnsonii*, *L. reuteri*, and *L. acidophilus* showed a 20 times elevated total free phenolic acid compared to the unfermented sample (Hole et al. 2012). Cheonggukjang fermented by *Bacillus pumilus* for 60 h generates 2.8-fold, 7.6-fold, and 4.5-fold increases in gallic acid, catechin, and epicatechin, respectively (Cho et al. 2009).

29.2.1 Role of Nutraceuticals from Fermented Foods in Cancer Prevention

Cancer is a complicated disease with different phenotypes and origins. About 5–10% of all cancer cases can occur due to genetic defects, whereas the remaining 90–95% have been observed for environment and lifestyle factors (Anand et al. 2008). Fermented soybean products are one of the richest sources of isoflavones, which act as a phytoestrogen in humans (Klejdus et al. 2005). The isoflavone content has been reported as follows: genistein 8 mg daidzein 0.5 mg and glycitein 7.2 mg per 100 g in fermented soybean (Nakajima

et al. 2005). Genistein is widely known for its anticancer effects (Cui et al. 2017). Chui et al. demonstrated that genistein significantly inhibited B16F10 cell proliferation and induced apoptosis in a time- and concentration-dependent manner. Genistein (100 μM) decreased the p-FAK, p-paxillin, tensin-2, vinculin, and α-actinin expression level, which finally regulates the FAK/paxillin and MAPK signaling pathways and regulates cancer progression (Cui et al. 2017). Genistein inhibited both the invasion of breast carcinoma cells and tumor growth in nude mice carrying MCF-7 and MDA-MB-231 xenografts by downregulating the matrixmettaloproteinase-9 (MMP-9), a gene involved in tumor cell migration (Shao et al. 1998). In a large, meta-analysis study, it is observed that soy intake was linked to lower incidence and mortality rate due to breast cancer (Chi et al. 2013). In another prospective cohort study of postmenopausal women, increasing amounts of daidzein consumption are responsible for reduced breast cancer recurrence (Guha et al. 2009).

Flavonols such as kaempferol and quercetin are abundantly found in Mulberry leaf extract which was fermented by *L. plantarum*, and these bioactive compounds have been involved in cancer prevention and progression (Lee et al. 2015a). The COX-2-catalyzed synthesis of prostaglandin E2 plays a key role in inflammation and its associated diseases and cancer (O'Leary et al. 2004). Quercetin and quercetin conjugates reduce COX-2 mRNA expression and activity in both unstimulated and Il-1β-stimulated $CaCO_2$ cells (O'Leary et al. 2004). Supplementing a diet containing quercetin (0–4.5 g/kg) suppresses the formation of early preneoplastic lesions in colon carcinogenesis by decreasing proliferation and increasing apoptosis (Warren et al. 2009). Besides, serum interleukin-6 (IL-6), a proinflammatory cytokine, is considered a sign of inflammation as well as colorectal carcinogenesis, which was found lower in participants taking flavonols, especially kaempferol and quercetin (Bobe et al. 2010). Kaempferol decreased cell viability and induced a G2/M phase cell cycle arrest in a concentration-dependent manner in SK-HEP-1 human hepatic cancer cells, which implies that kaempferol may be useful for long-term cancer prevention (Huang et al. 2013). Indole-3-carbinol (I3C) is another nutraceutical found in fermented cabbage (Tolonen et al. 2002). In C33A cervical cancer cells, I3C reduced Bcl-2 protein in a time- and dose-dependent manner (Chen et al. 2001).

Besides, cancer also develops through exposure to carcinogens. It is found that probiotics reduced the consumed carcinogens by several different practices, including emphasizing detoxification, improving apoptosis (programmed death of damaged cells), and inhibiting tumor growth (Aso and Akazan 1992). *Bifidobacterium breve* and *L. casei*, found in fermented foods like sauerkraut and kefir, both reduce intestinal absorption of toxicants such as bisphenol A. (Oishi et al. 2008). Bisphenol A has been shown to play a role in the pathogenesis of several endocrine disorders as well as hormone-dependent tumors such as breast and prostate cancer (Konieczna et al. 2015). Kimchi, a fermented cabbage dish, comprises probiotic strains that breaks down the organophosphorus pesticides by that toxin as food and breaks down sodium nitrate, a cancer-causing food preservative (Cho et al. 2009). Previously, fermented mung bean and soybean have been separately reported to have antioxidant, cytotoxic, and immunomodulatory effects (Ali et al. 2016). Nutraceuticals, for example, free amino acids and soluble phenolic acids (especially protocatechuic acid), were found in fermented mung bean. Both fermented mung bean and soybean products possessed cytotoxicity activities against breast cancer MCF-7 cells by arresting the G0/G1 phase followed by apoptosis. Moreover, they also induced splenocyte proliferation and enhanced serum interleukin-2 and interferon-γ to limit breast cancer cell proliferation (Ali et al. 2016).

29.2.2 Role of Nutraceuticals from Fermented Food for Metabolic Syndrome Prevention

Metabolic syndrome (MetS) characterizes a group of disorder including obesity, elevated

blood pressure, and impaired glucose metabolism, dyslipidemia, and cardiometabolic risk. The prevalence of metabolic syndrome is currently reaching epidemic proportions throughout the world (Wu et al. 2010). The treatment of MetS is basically dependent on an improvement of lifestyle, physical exercise, and a balanced low-energy diet.

Rice bran is a by-product of the rice milling process and a rich source of dietary fiber and numerous bioactive molecules like indole compounds (Islam et al. 2017). Fermented rice bran (FRB) prepared by dual fermentation of rice bran using *Aspergillus kawachii* and *Lactobacillus sp*. is effective against MetS observed in an animal model (Alauddin et al. 2016). Alauddin et al. (2016) showed that long-term supplementation of 5% FRB significantly reduced both systolic and diastolic blood pressure and improved leptin impairment and increased serum adiponectin levels and angiotensin-converting enzyme (ACE) inhibitory activity as well as insulin sensitivity. Besides, chronic FRB supplementation downregulated the gluconeogenesis and lipogenesis in the liver and alleviate MetS (Alauddin et al. 2016).

Monacolin K (lovastatin), a metabolite generated by Monascus, has been described as a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statins) with cholesterol-lowering action which is found in red mold rice (RMR). RMR is produced through the fermentation of ordinary rice with *Monascus* species. Water extracts of RMR suppress the glycerol-3-phosphate dehydrogenase (GPDH) activity and lipid accumulation, a marker of adipogenesis, in a dose-dependent manner in 3T3-L1 preadipocytes (Jeon et al. 2004). Animal study revealed that RMR (0.4 or 2%) doses for 6 weeks had lower weight gain and less fat pads mass accompanied with smaller fat cells compare to HF diet. Besides, RMR supplement considerably reduced serum total cholesterol and low-density lipoprotein (LDL) cholesterol and successfully prevented metabolic disorder in even providing high-fat diet (Chen et al. 2008).

Kimchi, another popular fermented food, contains beneficiary probiotic strain, notably lactic acid bacteria (Park et al. 2012). Park et al. demonstrated that 12 weeks of dietary intervention of HF-KCO (high-fat diet containing 3% kimchi manufactured with the starter culture *W. koreensis* OK1-6) on C57BL/6J mice significantly lowers the obesity by decreasing leptin and the mRNA expression level of liver X receptor α (LXRα), SREBP2, stearoyl-CoA desaturase-1 (SCD1), peroxisome proliferator-activated receptor γ (PPARγ), and CPT1 along with body and epididymal fat weight in the HF-KCO group compared to other control and HF diet group (Park et al. 2012). Red ginseng roots have bioactive compounds like saponins (ginsenosides) and nonsaponins (Oh et al. 2014). Both compounds have been recognized as potential compounds in maintaining blood glucose and insulin levels (Oh et al. 2014). Besides fermented ginseng roots (FGR) have elevated amount of saponins compared to nonfermented red ginseng (Oh et al. 2014). Study revealed that consuming 2.7 g/day of FGR for 4 weeks had reduced fasting and postprandial glucose, and increased fasting and postprandial insulin levels in human subjects (Oh et al. 2014). Kho et al. demonstrated that FRG 250 mg/kg/day for 8 weeks supplementation significantly reduced body weight, epididymal fat weight, and adipocyte size and prevented high-fructose-diet-induced hyperlipidemia and hypertension (Kho et al. 2016). FRG prevented endothelial dysfunction by downregulating endothelin-1 (ET-1) and adhesion molecules in the aorta as well as markedly upregulating the insulin receptor substrate 1 (IRS-1) and glucose transporter type 4 (Glut4) in the muscle and finally ameliorated MetS (Kho et al. 2016).

In addition, another Korean traditional fermented soybean pastes, called Doenjang, has investigated its protective effect against obesity and type 2 diabetes, where flavonoids and *Bacillus* probiotic strains are the major nutraceuticals (Kim et al. 2018). Long-term fermented soybean pastes (LFSPs) protects high-fat-diet (HFD)-induced nonalcohol fatty liver disease (NAFLD) and insulin resistance in obese mice. LFSPs improved glucose tolerance and increased adiponectin levels and attenuated HFD-induced gut permeability and lowered serum lipopolysaccharide (LPS) level to protect against NAFLD and insulin resistance (Kim et al. 2018).

Probiotics are also used as biotherapies during prevention of metabolic disorders (Mallappa et al. 2012). In a study, Kaddoka et al. (2010) revealed that probiotic LG2055 strain significantly reduced the abdominal adiposity and body weight in a study conducted with 87 high body mass index subjects who were randomly divided into two groups receiving either *L. gasseri* SBT 2055 (LG2055) or placebo and thus playing a role in obesity prevention.

Diabetes mellitus (DM) is another major health problem in the world. Type 2 diabetes is a complex metabolic disorder caused by insulin resistance, impaired insulin signaling and β-cell dysfunction, and abnormal glucose and lipid metabolism (Bahadoran et al. 2013). Elevated oxidative stress plays an important role in the occurrence and development of diabetes mellitus. Quercetin is well known for its antioxidative properties, abundantly present in the fermented onion (*Allium cepa*), when *Aspergillus kawachii* is used for fermentation (Yang et al. 2012). It has been reported that intraperitoneal-injected quercetin (15 mg/kg/day) reduced the oxidative stress and NO production and increased the antioxidant activity as well as maintain the pancreatic β-cell integrity in streptozotocin (STZ)-induced diabetes in rats (Coskun et al. 2005; Kim et al. 2007). Berries are considered as a rich source of bioactive phenolic compounds that can bind and prevent the enzyme dipeptidyl peptidase-IV (DPP-IV), a current target for type 2 diabetes therapy (Johnson and de Mejia 2016). Johnson and de Mejia extracted phenolic compounds like anthocyanins, predominantly delphinidin-3-arabinoside from fermented berry beverages which increased the insulin secretion from pancreatic β-cells *in vitro* by modulating DPP-IV and its substrate GLP-1 action (Johnson and de Mejia 2016).

29.2.3 Role of Nutraceuticals from Fermented Foods in Neurodegeneration and Anti-Aging

Aging is one of the key factors responsible for neurological disorder and enhanced neuroinflammation due to decrease antioxidant activity in the body. There is a growing interest toward the nutritional supplements like fermented food products or herbal medicines for the prevention and treatment of neurodegenerative diseases (Rehman et al. 2017). Anthocyanins are the major polyphenolic compounds found in fermented strawberry (Hornedo-Ortega et al. 2017), which prevented D-galactose (D-gal)-induced oxidative stress and elevated inflammatory response causing memory and synaptic dysfunction. Supplemented anthocyanins significantly improved behavioral performance by inhibiting activated astrocytes and neuroinflammation by suppressing inflammatory markers including p-NF- KB, inducible nitric oxide synthase (iNOS), and TNF-α in the hippocampus and cortex regions of D-gal-treated rats' brain (Rehman et al. 2017). Thus, anthocyanins could be an excellent nutraceutical for prevention of age-related neurodegenerative diseases such as Alzheimer's disease (AD) (Rehman et al. 2017). Monacolin k and gamma-aminobutyric acid (GABA) are the major active functional compounds that are isolated from red mold rice (RMR), which is being fermented by *Monascus purpureus* (Kim et al. 2016). GABA is the main inhibitory neurotransmitter in the central nervous system. Oral supplementation of GABA is an effective approach for memory performance and neurochemical profile in hippocampus of rats and can be used for the treatment of AD (Tabassum et al. 2017). Monacolin K also prevented amyloid beta peptide–induced neurotoxicity via repressing small G-protein-mediated inflammation, a potent synergism of anti-inflammatory and antioxidative effect in PC12 cell (Lee et al. 2008). Further, probiotics in fermented foods may also influence brain function via gut microbiota. Probiotic bacteria like *Lactobacillus* and *Bifidobacterium* strains are capable of producing GABA from glutamate (Barrett et al. 2012). Desbonnet et al. demonstrated that 14-day treatment of probiotics containing *Bifidobacteria infantis* on Sprague-Dawley rats significantly reduced the IFN-γ, TNF-α, and IL-6 cytokines and increased the plasma concentrations of tryptophan compared to control following mitogen stimulation (Desbonnet et al. 2008). Thus, *Bifidobacteria* treatment opens an

encouraging evidence that this probiotic may possess antidepressant properties. Therefore, it is hypothesized that fermented foods containing nutraceuticals might improve cognitive function by modulating the release of neurotransmitters (Desbonnet et al. 2008).

Isoflavone (genistein and daidzein) and β-glucan content were found elevated in fermented barley and soybean formula (BS) by yeast fermentation (Lee et al. 2015b). In a clinical study with BS-containing drink (3 g/day) for 8 weeks significantly improved the hyaluronan (HA) and skin barrier function *in vitro* and reduced Hyal2 expression in human dermal fibroblasts (HDF). BS also recovered ultraviolet (UV) B-induced downregulation of HA in HaCaT cells. Thus, BS has promising potential for development as a health functional food to enhance skin health (Lee et al. 2015b).

29.2.4 Role of Nutraceuticals from Fermented Food in Cardiovascular Disease Prevention

Cardiovascular disease (CVD) is the key cause of mortality and morbidity in the world (Micha et al. 2012). Major risk factors for CVD include presence of type 2 diabetes, dyslipidemia, obesity, and inflammation. Dietary components lessen CVD risk by attenuating associated risk factors, notably legumes. Diets containing fermented legumes are considered as a cardioprotective diet as they are associated with better weight management and glycemic control, reduced blood pressure, and a better plasma lipid profile (Bouchenak and Lamri-Senhadji 2013).

Nutraceuticals such as isoflavones, phytosterols, and lecithins are abundantly found in soybeans, which may act collectively or independently for cardioprotection (Ramdath et al. 2017). Dietary soy isoflavones increase arterial vasodilatation, improve endothelial function, and decrease blood pressure (BP), perhaps by nitric oxide (NO)-dependent mechanism in animal experiments (Mahn et al. 2005). Besides, this soy isoflavones also increase renal blood flow and sodium excretion, and interact with estrogen receptors to inhibit ACE activity in the renin–angiotensin–aldosterone system (Nagata et al. 2016). In an epidemiological study, it has been shown that there is an inverse association between consuming whole soy foods/products and CVD risk (Gil-Izquierdo et al. 2012). Same results were observed in dietary intakes of natto (fermented soy beans) and CVD mortality in Japanese adults, especially reductions in mortality from stroke by taking soy protein and natto (Nagata et al. 2016).

Isoflavones also decreased hypertension via endothelial vasodilation. In a study on postmenopausal women, isoflavone supplementation for 6 months increased endothelial vasodilation by significantly reducing cellular adhesion molecules (Colacurci et al. 2005). A reduction in SBP was found in pre- or hypertensive, mildly hyperglycemic postmenopausal women after taking isoflavones (100 mg), along with soy protein, for 6 months (Liu et al. 2013), although several studies found no effect on BP after intake of soy isoflavones (81–100 mg/day) for 6 weeks (Wong et al. 2012) or 1 year on menopausal women (Curtis et al. 2013).

Pigeon pea (*Cajanus cajan* L.) is another well-known grain legume crop in tropical and subtropical countries and contains high levels of phytosterol. Water extracts of *Bacillus subtilis*-mediated fermented pigeon pea has been shown to possess antidyslipidemic activity (Lee et al. 2015c). In an animal model, 100 mg/kg body weight of fermented pigeon pea significantly maintained both systolic and diastolic blood pressure (30 mmHg) in spontaneously hypertensive rats compared to nonfermented ones. Thus, *Bacillus*-fermented pigeon pea containing bioactive molecules is beneficial for cardiovascular disease prevention and can be used as a new source of nutraceuticals (Lee et al. 2015c).

29.2.5 Role of Nutraceuticals from Fermented Food in Ulcerative Colitis Disease Prevention

The occurrence and prevalence of inflammatory bowel diseases (IBDs) including ulcerative colitis (UC) and Crohn's disease are rapidly grow-

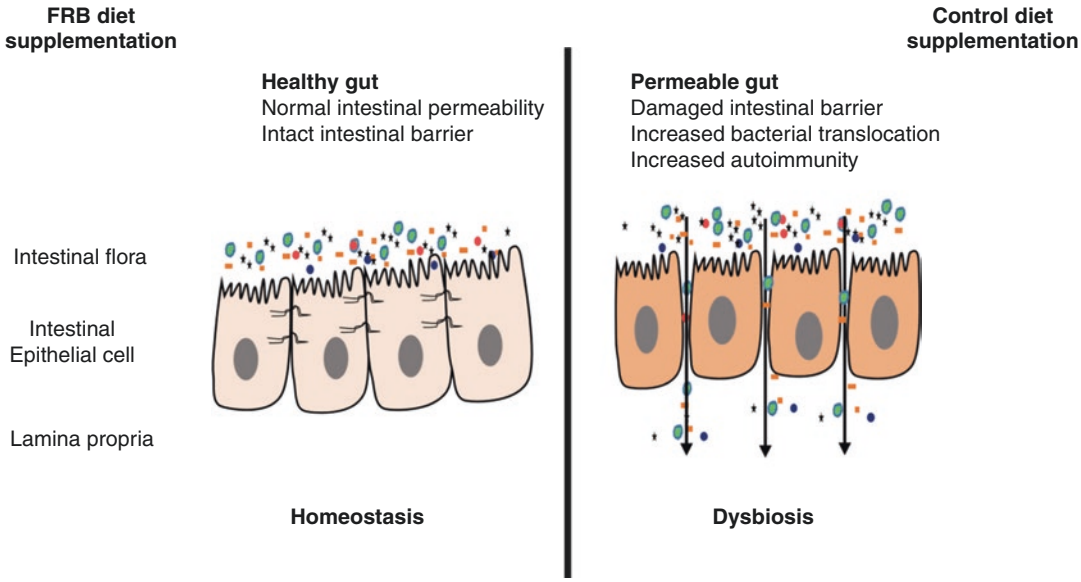

Fig. 29.1 Role of fermented rice bran in tight junctions (TJs) barrier integrity

ing in Western countries and in developed Asian countries (Kanai et al. 2014). It is a chronic immune disorder of unclear etiology (Islam et al. 2017). Environmental factors, especially lifestyle patterns for prolong intake of westernized diet (low fiber) resulting in the dysregulated composition of intestinal microbiota or dysbiosis, is responsible for its occurrence (Islam et al. 2017). Drugs that are used for suppressing the immune system have been effective in patients with IBD but termination of these drugs leads to relapse in the majority of patients (Kanai et al. 2014).

Fermented rice bran (FRB) is an excellent source of nutraceuticals like high fiber (Alauddin et al. 2016) and gut microbiome-induced short chain fatty acids (SCFAs) (Islam et al. 2017). Islam et al. explored the anti-colitis effect of FRB supplementation in a murine model of UC by 3% dextran sodium sulfate (DSS) and reported that the FRB-supplemented group significantly reduced the myeloperoxidase (MPO) and thiobarbituric acid-reactive substance levels and proinflammatory cytokine transcript (Tnf-a, Il-1b, Il-6, and Il-17) levels in the colon compared to the nonfermented group. Dietary FRB alleviated colitis via elevated production of SCFAs and tryptophan, which might regulate tight junction (TJ) barrier integrity and intestinal homeostasis (Fig. 29.1). Therefore, FRB could be a possible preventive dietary supplementation for UC (Islam et al. 2017). Hahm et al. demonstrated that fermented kimchi can significantly prevent DSS-induced colitis-associated cancer (CAC) in 12 weeks. Probiotics, *L. plantarum*, contained in the fermented kimchi, showed significantly inhibitory actions of IL-6, STAT3, and NF-κB, while in nonfermented kimchi, the involvement of probiotics and cancer prevention was highlighted (Hahm et al. 2018). Soy isoflavones such as genistein, daidzein, and its metabolite equol exhibit estrogen-like activity in the colon and enhance tight junctions (TJ) proteins and decrease proinflammatory cytokines production in experimental colitis (Verdu et al. 2002; Suzuki and Hara 2011). Woo et al. (2016) demonstrated the anti-colitis effects of fermented barley and soybean mixture (BS) on intestinal inflammation using a murine model of IBD. Orally administrated BS (100 and 200 mg/kg/day) for 3 days alleviated the severity of colitis by decreasing proinflammatory cytokines and epithelial barrier dysfunction, inducing an increase of TJ protein levels in colonic tissues. Supplementation of BS

increased the levels of *Lactobacilli* and *Bacteroides* in the gut, protecting against inflammatory bowel disease (Woo et al. 2016).

29.3 Conclusion

Fermented foods have excellent health-promoting benefits due to the presence of functional microorganisms and optimistic source of nutraceuticals. Fermented foods are treated globally as health foods and therapeutic foods, although sophisticated research is still needed to validate the health claims of fermented foods by clinical trials and animal model experiments. Consequently, there is a need to provide consumers with more information to effectively guide them in making wider choices of fermented foods that contain optimal levels of health-promoting nutraceuticals.

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