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REVIEW

Significance of Soy-Based Fermented Food and Their Bioactive Compounds Against Obesity, Diabetes, and Cardiovascular Diseases

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Abstract

Soybean-based fermented foods are commonly consumed worldwide, especially in Asia. These fermented soy-products are prepared using various strains of *Bacillus*, *Streptococcus, Lactobacillus*, and *Aspergillus.* The microbial action during fermentation produces and increases the availability of various molecules of biological significance, such as isoflavones, bioactive peptides, and dietary fiber. These dietary bio active compounds are also found to be effective against the metabolic disorders such as obesity, diabetes, and cardiovascular diseases (CVD). In parallel, soy isoflavones such as genistein, genistin, and daidzin can also contribute to the anti-obesity and anti-diabetic mechanisms, by decreasing insulin resistance and oxidative stress. The said activities are known to lower the risk of CVD, by decreasing the fat accumulation and hyperlipidemia in the body. In addition, along with soy-isoflavones fermented soy foods such as Kinema, Tempeh, Douchi, Cheonggukjang/Chungkukjang, and Natto are also rich in dietary fiber (prebiotic) and known to be anti-dyslipidemia, improve lipolysis, and lowers lipid peroxidation, which further decreases the risk of CVD. Further, the fibrinolytic activity of nattokinase present in Natto soup also paves the foundation for the possible cardioprotective role of fermented soy products. Considering the immense beneficial effects of different fermented soy products, the present review contextualizes their significance with respect to their anti-obesity, anti-diabetic and cardioprotective roles.

Keywords Fermented Soybeans · Bioactive Metabolites · Isoflavones · Obesity · Cardioprotective

Introduction

Soybean (*Glycine max*) has been known in southeastern Asian countries for more than 3,000 years. The key advantages are its high essential fatty acid content, protein content (all 8 essential amino acids), and abundance of minerals, vitamins, fiber, and isoflavones (daidzein and genistein) [1]. Further, soybean is widely used to prepare various fermented products in different countries, such as Korea, India, Japan, Myanmar, Thailand, China, and Indonesia. Only recently, health benefits of soybean were found to be associated with their phenolic bioactive compounds such as isoflavonoids (0.14–1.53 mg/g) [2]. Various microbial strains of *Lactobacillus*, *Streptococcus*, and *Bacillus* are prevalently used to ferment the soybean, increasing its biodigestibility and functional properties, for example fermented soy foods such as natto, tempeh, and soy sauce are richer in total isoflavones and aglycone isoflavones than their unfermented counterparts [2].

Obesity occurs due to excessive fat accumulation in the body through increased mass of the adipose tissue and enlarged fat cells, which further leads into metabolic disorders such as insulin resistance, low grade inflammation, oxidative stress and increased level of fatty acids [3]. The mentioned factors are also the etiology of type-2 diabetes, thus causing the parallel surge in obesity and diabetes [3]. In such escalated conditions, where glucose utilization is decreased, cardiac muscles depend on fatty acid oxidation for energy production, which causes the accumulation of lipids and hyperlipidemia, resulting in cardiovascular disease (CVD) [4]. On the other hand, fermented soy products

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can reduce the total cholesterol level in serum, and low-density lipoproteins (LDLs) [5]. In addition, fermented soy foods are rich in aglycone, a metabolically active glucose-free form of isoflavones, which has anti-oxidant activity [2]. The latter is negatively affects the obesity and diabetic conditions [6].

Fermented soy products are health-benefiting, and their effect is believed to be metabolite-driven but much information is not available in this regard. Therefore, preventive effects of various fermented soy meals and their constituents are discussed in this review article with an emphasis on obesity, diabetes, and cardiovascular disease in the context of chronic diseases. To address this, the present study meticulously examines and reports the regulatory role of fermented soy metabolites in obesity, diabetes, and CVD.

Soy-Based Fermented Foods and Their Importance

The major reluctance some consumers have for soy products is the inherent taste of soy products, described as bean-like/grassy or astringent and causing abdominal bloating. The first advantage of fermenting soy is that the beans become less flavorful and develop a typical taste due to bitter peptides produced during fermentation [7]. In addition, phytate (phytic acid) and oxalate (oxalic acid), present in soybeans inhibit the absorption of the essential mineral's calcium, iron, zinc, magnesium, and copper in the intestinal tract [8]. To combat that, fermentation process can minimize the anti-nutritional properties, unpleasant tastes, bloating, and sugars (stachyose and raffinose). This can be achieved through the use of microbial culture especially using lactic acid bacteria in the form of monocultures and polycultures. Probiotic fermentation of soy can lower the amount of gas-producing carbohydrates in the intestinal system and raise the levels of free isoflavones, changing the gut bacterial population in the gastrointestinal tract to benefit the host [9]. The beneficial qualities of soy food are present throughout microbial development, are created in the same way as other foods, proteolytic enzymes hydrolyze proteins into amino acids and peptides, oligosaccharides into monosaccharides, and phytate into inorganic phosphates [10]. These are the essential physicochemical characteristics of proteins that affect their behavior in the food system throughout production, processing, storage, and preparation.

The most common fermented soybean products are soy sauce, miso, natto, tofu, and tempeh. Miso means fermented bean paste and is used as a base and seasoning for soups. Miso making begins with boiling soybeans and inoculating it with a mixture of *Aspergillus oryzae* and *Aspergillus soyae*, upon cooling. Tempeh is the fermented product of shelled and cooked soybeans with *Rhizopus oligosporus* [11]. This fermentation results in cake-like product that is completely covered with mycelium and has a clean yeasty aroma. In vegetarian and Asian diets, tempeh is frequently served as a main meal or as a meat substitute. One of the foods most commonly consumed in Asia is soy sauce. In Japan only, the daily consumption is over 30 g/person/year and the annual consumption is over 10 L/person/year [12]. Soy sauces come in various varieties, each with unique qualities and production processes. Preparing basic materials (whole grain beans, soy flour, or soy flakes) and adding koji (an enzyme source, containing bacteria, mold and yeast) is the technique of preparing traditional soy sauce by the manufacturers. Similarly, locals of Khasi Hills of Meghalaya, India prepares a fermented vegetable protein prepared from soybean is known as *Tungrymbai* [13]. Other than that, kinema, hawaijar, bekang, aakhone, and peruyaan are a few of the popular ethnic non-salted sticky fermented soybean snacks of the Eastern Himalayas and are eaten in Nepal, the Eastern Himalayan region of India, and south Bhutan [14]. Soybean and its constituents have antioxidant, antidiabetic, antiproliferative, anti-obesity, and anti-inflammatory properties. Their consumption is associated with a variety of potential health benefits and a reduction in numerous chronic diseases such as immune disorders, cardiovascular disease, diabetes, obesity, and certain types of cancer (Table S1). Usually, the dietary impact of substances including fermented soy-products are examined using in vitro and in vivo approaches [15]. In the in vitro approach, the dietary substance is enzymatically digested and fermented according to the human body, and later produced gut-microbiome and metabolome are examined to conclude the effect of the substance [16]. Wherein, in the in vivo approach, animal models (mice, and humans) are used for dietary treatment, and later samples are collected to examine the impact. Other than metabolized by the human host, fermented soy food and their metabolites are also utilized by the gut microbes, making their effect more prominent [15].

Soy-Based Fermented Food and Their Role Against Cardiovascular Diseases

Cardiovascular diseases (CVD) are the leading cause of human death in the world. According to numerous studies, some dietary changes can reduce the risk of CVD by lowering associated risk factors. Further, the significance of legumes in a cardioprotective diet is emphasized in particular because increased intake is linked to better glycemic control, weight management, an improved plasma lipid profile by reducing Low-density lipoprotein (LDL) cholesterol, and lowered blood pressure [17]. In East Asian nations, foods made from fermented soy beans are significant sources of bioactive compounds (Table 1). These variety of distinctive bioactive chemicals are produced when cooked

Table 1 Effect of soy-based food, their association with cardiovascular diseases, and the role of soy metabolites in cardiac diseases. (*B* = *Bacillus; A* = *Aspergillus*)

Food name	Fermenting microorganisms and plants	Metabolite	Cardioprotective role	Reference
Tungrymbai	*Clinogyne dichotoma*	Aglycones, genistin, and daidzin	Antioxidant activity	[22]
Kinema	*Bacillus licheniformis, B. subtillis,* *B. cereus, B. thuringiensis, B. circulans, and B. sphaericus*	--	Decreases cholesterol and antioxidant activity	[23]
Hawaijar	*Bacillus licheniformis, B. cereus, B. subtilis, Staphylococcus aureus, Staphylococcus sciuri, Alkaligenes spp., Providenica rettgeri, Xanthomonas sp.*,	Trypsin, glutamine, cysteine, lysine, and leucine	Fibrinolytic activity	[24]
Natto	*Bacillus subtilis*	Nattokinase, vitamin K, levan, free isoflavones, and γPGA	Fibrinolytic and antithrombotic activity	[25]
Miso (soybean jiang) or Doenjang)	*Tetragenococcus halophilus, Staphylococcus sciuri Enterococcusfaecalis, B. subtilis, Citrobacter or Enterobacter*	Genistin, daidzin, glycitin, malonyl genistin, genistein, daidzein, non-DDMP-conjugated soyasaponins (I, III, Be), peptides, amino acids, MRPs, and kojic acid	Restores endothelial functions and normalizes flow-mediated vasodilation	[5]
Soy sauce (Ganjang)	*Aspergillus oryzae* or *A. sojae*	MRPs (Maillard reaction products), amino acids, peptides, 1-methyl-2,3,4-tetrahydro-β-carboline, and 1-methyl β-carboline	High antioxidant activity, anti-inflammatory, hypolipidemic effects, anti-platelet activity, anti-hypertension, and anti-allergenicity	[26]
Tofu	*Lactobacillus curieae*	Genistin, glycitin, malonyl genistin, genistein, and daidzein	Isoflavones restore endothelial functions and normalizes flow-mediated vasodilation	[5]
Douchi	*Aspergillus oryzae*	Subtilisin DFE, isoflavones, and peptides	Antioxidant, anti-acetylcholine esterase fibrinolysis, and antidiabetic. Restores endothelial functions and normalize the Flow-mediated vasodilation	[27]
Cheonggukjang or Chungkukjang	*Bacillus amyloliquefaciens, B. cereus*, and *B. subtilis.*	Genistin, malonyl genistin, daidzin, glycitin, genistein, and daidzein	Isoflavones restore endothelial functions and normalizes flow-mediated vasodilation	[5]
Tempeh	Fibrinolytic microorganisms such as *Staphylococcus sciuri, Bacillus subtilis, Enterococcus faecalis*, and *Citrobacter*, or *Enterobacter*	6,7,4'-trihydroxyisoflavone, isoflavones, peptides, daidzein and genestein	BACE1 inhibition, antioxidant, and cognitive improvement	[28]
Gochujang or Kochujang	*Aspergillus oryzae*	Capsaicin and free isoflavones	Antioxidant, anti-hypersensitive, and anti-obesity	[29]
Fermented soymilk	*Bifidobacteria*	Water-soluble vitamins (B2, B6, folate and B12), vitamin K2 and free isoflavones	Antioxidant, anti-mutagenic, increased mineral bioavailability, hypo-cholesterolemic effects, and anti-obesity	[30]

soybeans are fermented and many of which have significant health benefits (Table 1**)**.

The bioactive component of soybean foods, in particular isoflavones, can work in conjugation with proteins to maintain cardiovascular health [18]. Other than that, fermented soy meals contain isoflavones in the form of aglycones (genistein, daidzein, and glycetein). Among those genistein is the dominantly found isoflavone in soybean and is supposed to be the most bioactive compound. Isoflavones from fermented soybean products have both anti-estrogenic and estrogenic effects, depending on the tissue in which they act [19]. One of the proposed mechanisms by which soybeans reduce heart disease is by lowering cholesterol [18]. A study comparing isoflavone-depleted soy protein and isoflavone-rich protein on mildly hypercholesterolemic and postmenopausal women's plasma lipid concentrations, showed that soy protein high in isoflavones reduced the total and LDL cholesterol more than soy protein low in isoflavones [20]. However, there were minor variations in the amounts of triacylglycerol or high-density lipoprotein (HDL) cholesterol. The difference in the above two soy protein supplement's ability to lower total and LDL cholesterol points to a possible contribution from the isoflavone-containing portion [21].

Natto is a traditional Japanese fermented soy food that is made by fermenting soybeans with the bacteria *Bacillus* *subtilis var. natto.* Fermented natto is found to be rich in enzyme nattokinase, an extracellular subtilisin-like serine protease with strong atherosclerosis and anti-hyperlipidemic properties [31]. In a study of 76 patients who were supplemented with oral nattokinase, there was a decrease in total cholesterol, plaque size, and total LDL cholesterol hence proving the effectiveness of natto in declining cholesterol and its associated lipids [32]. Food made from fermented soy can also work as an anti-lipid peroxidative molecule to alleviate obesity/diabetes as decreased lipid peroxidation is associated with the lower levels of antioxidants and oxidative stress. A similar study also revealed that soybeans fermented with *Aspergillus oryzae* have high antioxidant levels and can inhibit lipid peroxidation [33]. In addition, Natto exhibits strong fibrinolytic activity, in a Japanese study, participants who consumed natto (200 g) daily for two weeks as part of a human experiment displayed shorter plasma clot lysis time, which is a sign of increased plasma fibrinolytic activity [34]. Apart from nattokinase, Natto has also been reported to contain various biologically active factors with fibrinolytic activity, such as dipicolinic acid, bacillopeptidase F [35]. Although clinical investigations are still required to identify the precise mechanisms underlying antithrombotic effects of nattokinase.

Similarly, *Bacillus* fermented soy milk contains peptides that may have antihypertensive properties [36]. In an experiment, *Bacillus* was used to brew soy milk and examined for numerous aspects, including total peptide content and systolic blood pressure (SBP). The observations showed that increased peptide content could lower SBP, making it one of the factors in blood pressure control and maintenance. The appearance of hyperlipidemic and low-grade inflammation conditions in atherosclerosis further demonstrates the close relationship between inflammation and hyperlipidemia in many pathological conditions [36]. A recent study showed that the fatty acid profile in the skin of rats was improved by fermented soy milk, which inhibits the expression of inflammatory genes induced by cholesterol [37]. This investigation of pro-inflammatory cytokines, including inducible cyclooxygenase-2 (COX-2), nitric oxide synthase (iNOS), and interleukin-1 (IL-1), revealed that soymilk administration dramatically reduced IL-1 expression levels in rats with inflammation [37]. Moreover, when the soybean fermented products were administered, a change in the NF-kB pathway, which is crucial for inflammation, is also observed.

Cheonggukjang, also spelled as chungkukjang, a traditional Korean fermented soy food prepared from the fermentation of cooked soybean with *Bacillus subtilis* has been shown to possess anti-inflammatory properties [38]. An in-vitro study also supports the cardioprotective effect of cheonggukjang-induced gut-microbiome by enhancing the beneficial *Coprococcus*, *Ruminococcus*, and *Bifidobacterium* and by lowering the pathogenic *Sutterella* [15]. A recent investigation on male rats with diet-induced obesity (DIO) suggested that the AKT/mTORC1 pathway is a possible mechanism through which soy isoflavones can control lipid metabolism [39]. Moreover, soy isoflavones have extraordinary effects on adiposity, as they can decrease body weight, lipid accumulation in the liver, adipogenesis, and lipogenesis, as well as improve *β*-oxidation and lipolysis [40]. Doenjang is another Korean fermented soy product that is produced from fermented soybeans with *Rhizopus spp., Aspergillus spp.*, and *Bacillus subtilis* [41]. The study on Doenjang suggests that it decreases the cholesterol and lowers the lipid peroxidation parameters [42].

Another traditional Korean soy food Kochujang (Gochujang), demonstrated a potent hypocholesterolemic effect in humans, as it decreased the levels of both total cholesterol and LDL cholesterol levels [43]. The peptides from soy βconglycinin (peptide 3 and peptide 2) were shown to have a hypocholesterolemic impact in another intriguing study on HepG2 cell lines [44]. The properties of these two peptides, YVVNPDNNEN (peptide 3) and YVVNPDNDEN (peptide 2), are similar to those of statins, that inhibit the production of endogenous cholesterol while preventing the activity of the enzyme hydroxymethylglutaryl-CoA (HMG-Co-A) reductase. Additionally, peptides 3 and 2 increase the levels of the low-density lipoprotein receptor (LDLR) protein by activating SREBP2, which increases the LDL degradation in liver [45]. Kochujang also activates the Peroxisomes proliferator activated receptor-2 (PPAR-2) gene, which regulates lipid metabolism and is linked to obesity. In HepG2 cell lines, soy peptides are also found to control the cholesterol homeostasis [46]. These findings also suggests that the ability of soy protein to lower cholesterol levels may be attributable to its capacity to reduce LDL formation, which may be accomplished by altering the amounts of apolipoprotein B in HepG2 cell lines [47]. Several other studies on Kochujang indicated that it can lower the blood triglyceride, blood sugar, cholesterol levels, and the development of lipogenic enzymes, while boosting the expression of lipolytic thus inhibiting the obesity [48]. Another soy-based probiotic beverage, kefir, contains high isoflavone aglycone, which lowers LDL cholesterol and prevents obesity [49]. Additionally, it prevents the accumulation of pro-inflammatory markers in plasma [19]. Figure 1 summarizes the cardioprotective role of fermented soy metabolites and their impact. Atherosclerotic lesion is characterized by the accumulation of plaque in the inner walls of arteries, typically consisting of cholesterol, fats, cellular debris, and other substances. These lesions can narrow and harden the arteries, leading to reduced blood flow and an increased risk of various cardiovascular diseases. Bioactive compounds found in fermented soy foods play a significant role in mitigating

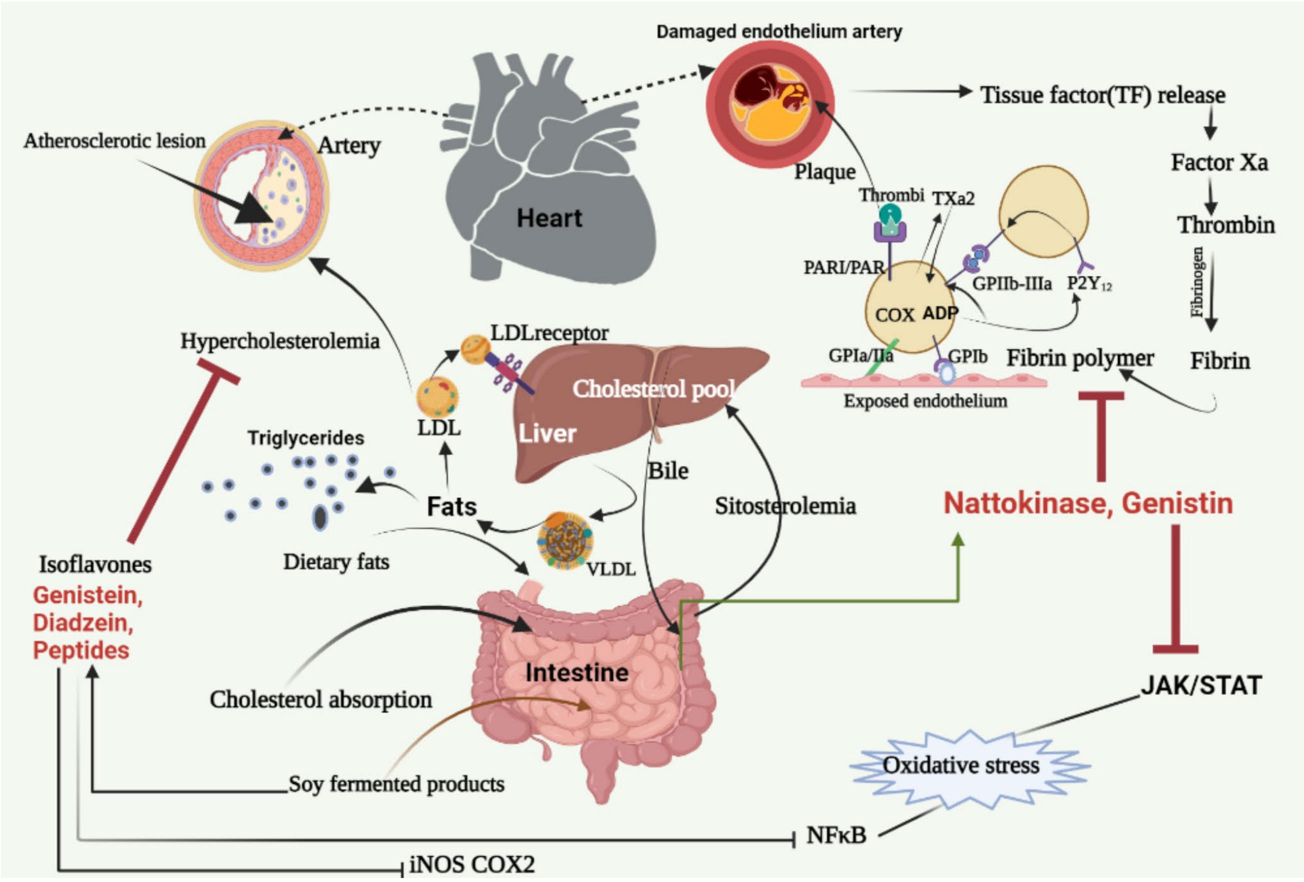

Fig. 1 An overview of the bioactive ingredients found in soy-fermented products and their potential applications in the treatment of cardiovascular diseases like atherosclerosis, oxidative stress, and arterial thrombus formation

hypercholesterolemia. Key components such as isoflavones, genistein, daidzein, and peptides are instrumental in preventing the clogging of blood vessels (Fig. 1) [5]. Furthermore, these bioactive constituents aid in shielding the body from damage caused by oxidative stress. Particular, nattokinase and genistin contribute to preventing the formation of plaque in damaged endothelial arteries by inhibiting signal transduction and fibrin polymer aggregation (Fig. 1).

Further, soy-based probiotics have an impact on the immune system and gut microbiota by increasing IL10 and IL6 levels, and by activating the fatty acid oxidation gene PPAR in both the adipose tissues and liver. In addition, fermented soybean products have been linked to possible antidiabetic effects in post-menopausal women as they contain substances like phytoestrogen, bioactive soy peptides, and iso-flavonoids [6]. They lower blood glucose levels by stimulating more beta cells for insulin production.

Soy-Based Fermented Food and Their Role Against Obesity and Diabetes

Role of Obesity and Diabetes in the Development of Cardiovascular Disease

Clinical and experimental studies have revealed that type 2 diabetes is more likely to develop in those who are overweight or obese (T2D). People with T2D have a higher risk of developing cardiovascular problems even with proper cholesterol, glucose, and blood pressure control [50].

Not all patients who are overweight or obese show the expected changes in cardiovascular risk factors, even though greater body mass has been associated with a higher incidence of altered cardiovascular risk factors. Obesity and coronary atherosclerosis are closely related as studies on young adults have revealed that atherosclerosis begins ten years before coronary artery disease manifest itself. cardiovascular risk factors. Obese individuals have a higher frequency and severity of atherosclerotic vascular lesions than the patients with normal body weight. Obesity has a higher chance of becoming a standalone risk factor for coronary artery disease if it has persisted for at least two decades. Furthermore, obesity also encourages platelet aggregation, endothelial dysfunction, interstitial cardiac fibrosis, aldosterone levels, and mineralocorticoid receptor expression [51]. Obesity causes an imbalance in the adipokines that are released by the adipose tissues, which leads to cardiovascular diseases and generalized metabolic dysfunction. Obesity also increases the expression of pro-inflammatory adipokines while decreasing the assembly of anti-inflammatory adipokines. Furthermore, due to the imbalance in adipokines, the regulated microenvironment of adipose tissue, and communication, the heart gets dysregulated, which leads to the emergence of a chronic low-grade inflammatory state [52]. Contrarily, a meta-analysis of the relationship between obesity and heart failure incidence revealed that each 10-cm increase in waist circumference is associated with a higher occurrence of heart failure [53]. An ongoing sugar intake can cause prolonged hyperglycemia; as a result, advanced glycation end products, or AGEs, are produced. AGEs are non-enzymatic glycation products of proteins and lipids that cluster in the vessel wall and damage the extracellular matrix's structural integrity. Further outcomes include the reduction of NO activity, endothelial damage, and diabetes complications that cause CVD [54].

Impact of Fermented Soy Foods on Diabetes and Obesity

Diabesity is directly related to oxidative stress (OS). The bioactivity of nitric oxide (NO) is decreased by free fatty acids, and endothelial cells' mitochondrial enzymes and electron transport chain complexes control the production of reactive oxygen species (ROS) in response to free fatty acid signaling pathways that promote inflammation. Furthermore, when stress pathways are engaged, prolonged exposure to ROS has a detrimental impact on insulin signaling, causing insulin resistance [6]. Consuming foods high in isoflavones is thought to be a potential approach in treating diabetes and obesity [44]. Genistein alleviates insulin resistance and thus lowers the risk of diabetes by minimizing the state of inflammation in overweight people, and by reducing the reactive oxygen species (ROS). After consumption, genistein increases the generation of proteins such as insulin receptor substrate (IRS) 1, c-JUN N-terminal kinase, and glucose transporter (GLUT) type, boosts superoxide dismutase, and reduces mitochondrial damage and lipid peroxidation. Daidzein, a substance also found in soybeans, stimulates the IRS1 and GLUT4 genes in adipocytes to increase the absorption of glucose in response to insulin [55].

Several studies have demonstrated that modifying one's diet can prevent and treat a variety of metabolic imbalances such as dyslipidemia, central obesity, and high fasting glucose [6]. Simultaneously, on the other hand, studies have shown that the isoflavones genistein and daidzein, which are present in abundance in fermented soybean meals, induce thermogenesis and influence lipid synthesis. Metabolites such as aglycones, act as agents that work against obesity via lipogenesis, hyperglycemia, hyperlipidemia, and improved insulin resistance. According to some studies, these effects are due to the bioactive phytochemicals present in fermented soybean foods, including hemagglutinin, protease inhibitors, alpha-glucosidase, alpha-amylase inhibitors, and crude fibers, which can disrupt normal metabolism and help treat obesity and other metabolic diseases [56] (Figure S1).

Obesity also has been associated with the menopausal transition among women, which begins with the pre-menopause period and ends with the post-menopause period. Several disorders are associated with a greater risk during this stage because of the lack of hormonal regulation, including hypertriglyceridemia, elevated blood pressure, abdominal fat accumulation, decreased high-density lipoprotein cholesterol (HDL-C), high levels of low-density lipoprotein cholesterol (LDL-C), and diabetes or decreased glucose tolerance. As a result of their structural and functional resemblance to estrogen, high levels of isoflavones exhibits beneficial effects on women's lipid profiles and body fat distribution through the menopause period [44]. It has been shown that low-glycemic diets can minimize insulin as well as glucose levels, lower the risk of type 2 diabetes, and limit weight gain. Both model animals and human trials have demonstrated the hypoglycemic effects of fermented meals [57]. Fermentation can lower concentrations of soluble carbs and can enhance levels of resistant starch and dietary fiber. For example, lactic and acetic acids created during sour dough fermentation help to reduce the amount of available starch and postpone gastric emptying, which in turn lowers the glycemic index [58].

In the past, multiple studies have tested the suitability of traditionally fermented soy meals as a potential alternative medication to address this global health concern on diabetes indicators (Table 2). Among the results obtained to date are, reduced insulin and blood sugar levels, enhanced insulin sensitivity in the liver, lower cholesterol and triglyceride levels, reduced oxidative stress levels, and regulated glucose homeostasis. It has also been shown that these foods enhance the absorption of aglycones-isoflavone-like genistein, which helps reduce inflammatory cytokines and reactive oxygen species (ROS). Even while the majority of the studies under analysis provided encouraging results for important obesity indicators (the percentage of body and visceral fat, waist-hip index, weight, and waist circumference), some of them clearly improved the lipid profiles of their subjects. (Figure S1). Still further studies are required to demonstrate the mechanism of isoflavones, soy peptides,

Table 2 Fermented soy product and their effect on obesity and diabetes (*B.* = *Bacillus, L.* = *Lactobacillus, S.* = *Streptococcus)*

Food name	Fermenting microorganisms and plants	Metabolite	Role against obesity/Diabetes	References
Natto	*B. subtilis var. natto*	Anthocyanins, isoflavones, dietary fiber, vitamins, and linoleic acid	1. Improves cholesterol and insulin sensitivity 2. Reduces oxidative stress, low-density lipoprotein in overweight people	[60]
Fermented soymilk	*Bifidobacteria*, Kefir culture (*L. plantarum*, *L. casei*, *Leuconostoc cremoris*, *S. diacetylactis, S. lactis*, *S. cremoris*,	Tyrosol, taurine, genistein, daidzein, isoflavone, GABA, acetate, isovalerate, and 2-methylbutyrate	1. Antioxidant effect against people with renal disease with type 2 diabetes	[61]
Meju	*B. subtilis, B. licheniformis, B. cereus, B. megaterium, Monascus sp., Penicillium expansum, P. roqueforti, Fusarium fujikuroi, Fusarium cf. incarnatum, Aspergillus cibarius, A. fumigatus*, and *A. oryzae*	Phenylalanine, glutamic acid, leucine, adenine, tryptophan, proline, acetylornithine, valine, isoleucine, pipecolic acid, methionine, citric acid, tyrosine, citrulline, arginine, glutamine, γ-aminobutyric acid, xanthine	1. Decreases the glucose concentration in diabetic rats 2. Prevent body's weight gain 3. Decreases leptin levels and serum triglyceride in obese mice	[62]
Chungkookjang	*B. lichemiformis, B. cereus, B. amyloliquefaciens*, and *B. subtilis*	Aglycone, isoflavones, genistein, 3-hydroxy-genistein, and equol 7-glucuronide, isoflavonoid aglycones, and small peptides Fr-2-2 and Fr-2-3	1. Improves the blood and hepatic glucose, lipid metabolism, and increases the pancreatic beta-cell functions and fatty acid oxidation in the liver	[63]
Douchi	*Zygosaccharomyces rouxii, Aspergillus oryzae, Bacillus subtilis*, and *Lactobacillus plantarum*	8-hydroxydaidzein and 8-hydroxygenistein	1. Antidiabetic effect (anti β glycosidase activity) 2. Antioxidant and Antihypertensive activity	[64]
Miso	*Aspergillus oryzae*, LAB *Tetragenococcus halophilus* and the yeast (*Zygosaccharomyces rouxii, Wickerhamomyces anomalus)*, Aerobic species *(Staphylococcus gallinarum*), *Enterococcus faecium*	Isoflavones and fiber aglycone forms genistein and daidzein	1. Decreases serum aspartate transaminase and body weight, lipid peroxidation in the liver. Suppresses visceral fat accumulation. 2. Increases the expression of Hsl (lipase, hormone-sensitive) involved in lipolysis and the expression of PPAR-γ	[65]
Tempeh	*L. plantarum, L. fermentum, L. reuteri, L. lactis, Rhizopus oligosporus B. subtilis, Staphylococcus sciuri, Enterococcus faecalis, and Citrobacter*	Daidzein, genistein, beta-sitosterol, Isoflavone aglycones, free amino acids, and peptides	1. Regulation of blood glucose levels and type 2 diabetes 2. Protection against cardiovascular disorders	[66]
Kinema	*B. subtillis, B. thuringiensis, B. licheniformis, B. cereus, B. circulans, B. sphaericus, Enterococcus faecium, Candida parapsolosis*, and *Geotrichum candidum*	Chrysin, swainsonine, benzimidazole (antimicrobial, anticancer, and anti-HIV activities), and 3-hydroxy-L-kynurenine (anticancer activity)	1. Reduces the cholesterol level	[5]
Doenjang	*Tetragenococcus halophilus, Bacillus aryabhattai, B. licheniformis, B. methylotrophicus, B. siamensis, Enterococcus faecalis, E. faecium, Staphylococcus equorum, Staphylococcus nepalensis*, and *Staphylococcus saprophyticus*	Isoflavones, phytoestrogen, genistein and daidzein	1. Increases ability to secrete insulin 2. Prevents the buildup of visceral fat brought on by diet, potentially as a result of its effects on increasing carnitine palmitoyl transferase (CPT)-1 activity and decreasing fatty acid synthase (FAS) activity	[67, 68]
Kochujang or Gochujang	*B. velezensis, B. amyloliquefaciens*, and *B. subtilis*, *B. licheniformis* and *B.* velezensis, *Zygosaccharmoyces rouxii*, *Z. beilli*, and *Candida apicola*, *Aspergillus oryzae*	Capsaicinoid, and genistein	1. Reduces the storage of hepatic fat, serum leptin levels, visceral fat, body weight and stimulates the lipolysis 2. Improves insulin sensitivity leading to improved glucose tolerance	[43, 69]

Table 2 (continued)

Food name	Fermenting microorganisms and plants	Metabolite	Role against obesity/Diabetes	References
Hawaijar	*B. subtilis, B. licheniformis, B. amyloliquefaciens, B. cereus, Staphylococcus aureus, Staphylococcus sciuri, Alkaligenes species, Providencia rettgers*, and *Proteus mirabilis*	Isoflavones and proteins/peptides	1. Reduces fasting blood glucose, glycated hemoglobin, insulin resistance, and body weight	[44]
Bekang and, Tungrymbai	*B. subtilis, B. coagulans, B. brevis, B. circulans, B. licheniformis, B. pumilus, B. sphaericus*, and *L. fusiformis*	--	1. The synthesis and breakdown of polyglutamic acid (PGA) 2. Antioxidant and free radical (DPPH and ABTS) scavenging activity	[70]

and fermented soybean products affecting cell mass, glucose metabolism, and insulin resistance [59].

For example, Doenjang contains genistein and daidzein, which may reduce cholesterol and lower the risk of a heart attack [71]. The active components found in *Bacillus* probiotic strains in Doenjang, were found to enhanced glucose tolerance via promoting the enzyme carnitine palmitoyl transferase (CPT)-1, which efficiently decreased the activity of the enzyme fatty acid synthase (FAS) [51]. Doenjang also enhances the production of adiponectin, which inhibits nuclear factor-B, a transcription factor associated with fat, from being expressed [68].

Cheonggukjang/Chungkukjang supplementation enhanced lipid metabolism, decreased body fat buildup, and raised the mRNA expression of proteins and fatty acid oxidation enzymes in the liver of mice fed a high-fat diet. *Bacillus subtilis* increases the IRS2-AKT pathway's activity and lowers the expression of phosphoenolpyruvate carboxykinase (PEPCK) in type 2 diabetic rats to increase hepatic insulin signaling [21]. In addition, cheonggukjang has also been reported to control blood glucose levels and enhance pancreatic beta-cell activity in C75BL/KsJ-db/db mice [72]. Another fermented soy food, Touchi contains glucosidase that inhibits the small intestine's processing of carbohydrates, lowering the blood glucose and plasma insulin spikes that come with meals. A traditional Indonesian fermented soy food, tempeh, can boost isoflavone and probiotic levels while also lowering the content of fat. These lower the blood sugar, total cholesterol, and body weight to improve type II diabetes. It is considered that the enhanced antioxidative and glycolytic enzyme (glycosidase and amylase) inhibitory activity caused anti-obesity effects.

Conclusion

Fermented soy products such as Tempeh, Kinema, Natto, Cheonggukjang, Doenjang, Douchi have benefits that go beyond nutrition and can be used to prevent as well as cure diseases such as obesity, diabetes and mild CVD ailments. Fermented soy food contains various beneficial bioactive substances including biopeptides, isoflavones, and flavonoids, having health benefiting roles like antidiabetic, ACE-inhibitory, anti-tumor, and antioxidant properties. Bioactive compounds/peptides found in fermented soybeans have been the subject of an expanding body of research that has led to their use as pharmaceuticals with specific health benefits such as nattokinase in case of CVD. These compounds also serve as an alternative to synthetic drugs that may possess side effects. Peptides are one of the intriguing components in fermented soybean products that may promote health, according to studies conducted so far. In addition, soy metabolites are found to be specially beneficial for postmenopausal women as soy metabolites can be utilized by the gut communities to generate phytoestrogens, which are similar to estrogen and can ease the postmenopausal ailments such as obesity and type 2 diabetes. Fermented soy foods are also found to beneficially alter the gut microbiome and increasing the abundance of beneficial microbes to support the host health. To further elucidate the impacts, metagenomics, whole genome sequencing (WGS), and metabolomics can be used in future studies on fermented soy meals to explore their microbiota and their metabolites. Simultaneously, large-scale human trials will also be required to show the health benefits of these soy-based fermented foods.

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Data Availability Not applicable.

Declarations

Ethical Approval Not applicable.

Conflict of Interest Authors have no conflict of interest to declare.

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