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Review

Glucoregulatory Properties of Fermented Soybean Products

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Abstract: Type 2 diabetes mellitus is a chronic metabolic disease, characterized by persistent hyperglycemia, the prevalence of which is on the rise worldwide. Fermented soybean products (FSP) are rich in diverse functional ingredients which have been shown to exhibit therapeutic properties in alleviating hyperglycemia. This review summarizes the hypoglycemic actions of FSP from the perspective of different target-related molecular signaling mechanisms in vitro, in vivo and clinical trials. FSP can ameliorate glucose metabolism disorder by functioning as carbohydrate digestive enzyme inhibitors, facilitating glucose transporter 4 translocation, accelerating muscular glucose utilization, inhibiting hepatic gluconeogenesis, ameliorating pancreatic dysfunction, relieving adipose tissue inflammation, and improving gut microbiota disorder. Sufficiently recognizing and exploiting the hypoglycemic activity of traditional fermented soybean foods could provide a new strategy in the development of the food fermentation industry.

Keywords: fermented soybean; type 2 diabetes mellitus; glucose homeostasis; target tissues; mechanisms

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1. Introduction

Diabetes mellitus (DM) is a non-communicable, chronic metabolic disorder characterized by hyperglycemia, defects in insulin secretion, and insulin action, which has become a major public health issue worldwide with significant economic and social implications [1]. Of the three major types of diabetes, type 2 diabetes (T2DM) is far more common (accounting for approximately 90% of DM cases) than either type 1 diabetes mellitus or gestational diabetes [2]. The global burden of T2DM has risen substantially in the last 20 years, affecting more than 463 million individuals globally [3]. T2DM is primarily caused by two interrelated factors: (1) cells in muscle, fat, and the liver become resistant to insulin; (2) defective insulin secretion by pancreatic beta-cells [4]. Drug therapies are available but are associated with various side effects such as several hypoglycemia, muscle pain, disturbed mitochondrial function, and bladder cancer [5]. Thus, developing food-derived alternatives to oral hypoglycemic drugs without side effects or toxicity is of practical importance [6]. Increasing evidence suggests that food-derived bioactive compounds have vast potential in the mitigation of T2DM [7].

Soybeans have long been an indispensable part of a healthy diet in many Asian countries mainly due to the high contents of proteins (38–42%), oil (20–30%), and some phytochemicals. Phytoestrogens and proteins in soybeans seem to have beneficial actions

both on glucose metabolisms, and additional micronutrients such as saponins, phytosterols, trypsin inhibitors, as well as the amino acid and protein composition, may have additive or synergistic effects [8]. The high biological value of soy protein makes it nutritionally commensurable to animal proteins like casein, egg, and beef [9]. Many epidemiological studies have demonstrated the benefits of soybean products in lowering the risks of T2DM, cardiovascular diseases, and cancers such as breast, prostate, and colon cancers [10]. Soybean is consumed in both unfermented (roasted and fried soybeans, soybean powder, soybean butter, soy milk, tofu, soybean oil, etc.) and fermented (*soy sauce*, *tempeh*, *natto*, *douchi*, *doenjang*, etc.) forms [11,12]. However, it should be noted that the presence of anti-nutrients (e.g., agglutinins, phytochemicals, saponin, and protease inhibitors) in soybeans can interfere with the digestion, absorption, and metabolism of nutrients, thereby limiting the nutritional values of soybean foods [13]. Fermentation, however, can improve the physicochemical properties, sensory quality, and nutritive value of soy foods [14,15].

Fermented soybean foods are one of the most popular consumed foods in Asian countries, such as *douchi*, *sufu*, *soy sauce*, *doubanjiang* in China, *meju*, *cheonggukjang*, *doenjang*, *kanjang* in Korea, *natto*, *miso*, *tofuyo*, *shoyu* in Japan, *tempeh* in Indonesia, *thua-nao* in Thailand, *kinema*, *hawaijar*, *tungrymbai* in India (Figure 1) [12,16]. Soybean fermentation also results in the release of new bioactive components (e.g., peptides, isoflavonoids) by the action of proteolytic enzymes produced by the microorganisms involved during fermentation [17]. After fermentation, isoflavonoid glycones are changed into isoflavonoid aglycones, which seem to have greater activity than do isoflavonoid glycones [8]. Many of these components are believed the major contributors to the health benefits of fermented soybean products (FSP) [18]. Indeed, consumption of FSP, but not unfermented soybeans, has been reported to have therapeutic properties for T2DM [8,19–21]. This review aims to summarize the promising antidiabetic properties of FSP and to dissect how the FSP acts over a variety of molecular targets such as carbohydrate digestion and intracellular signaling pathways in multiple organs to maintain glucose homeostasis.

2. Traditional Fermented Soybean Foods: Processing and Products

Traditional fermented soybean products have a long history and are very popular in many countries. According to records, China was the first country to produce FSP, with *douchi*, *dajang*, *sufu*, and *soy sauce* as the representative products. These FSPs were introduced to Japan, Korea, Philippines, Indonesia, and other southeast Asian countries and regions in the early stages, and have further evolved with local characteristics, such as the famous Japanese *natto* and *miso*, Korea *doenjang* and *cheonggukjang*, and Indonesian *tempeh* [22]. China, Japan, and Korea are the leading producers of FSP worldwide. Although FSP originated in Asia, these products are consumed, popularized, and produced worldwide as Asian food has prospered globally. Moreover, FSP are believed to have health-promoting effects such as anti-diabetes, anti-oxidant, anti-inflammatory, anti-obesity, and anti-cancerous effects. Because of their healthy functions, these fermented foods have recently gained popularity [23].

Fermentation of soybean gives rise to different products based on many criteria, but mainly due to the microorganism used in the process as they affect the aroma, texture, therapeutical, and nutraceutical values. *Bacillus* spp., lactic acid bacteria (LAB) and fungi (i.e., *Aspergillus oryzae*, *Mucor* spp. *Rhizopus* spp., and *Fusarium* spp.) are reported to be the key players in FSP [12,24]. Some of the FSP are fermented only with bacteria (*natto*, *chungkookjang*, *kinema*); some are fermented solely with fungi (*douchi*, *tempeh*, *sufu*, *miso*, *tofu*) and in some cases, both microorganisms are used (*doenjang*) (Figure 2A) [12]. Records of production methods were found in *Qimin Yaoshu* (Essential Techniques for the Peasantry), a magnum opus of historically significant Chinese manuscript dating back to 533–544 AD, and others in the Korean manuscript *Samkuksaki*, dating from the 1392s, pointing to the consumption of fermented soybeans since the 12th century [24]. FSP are usually made from soybeans and wheat. Generally, an open process of single-strain or multi-strain mixed fermentation is adopted, which mainly includes two steps of koji making and post-fermentation [22,25].

Figure 2B depicted the common production process of FSP. Firstly, the raw materials are pretreated (sorting and soaking). Then, they are heated at high temperatures, where starch is thoroughly gelatinized, and protein is moderately denatured. After that, starter cultures (for example, *Aspergillus oryzae*, *Zygosaccharomyces rouxii*, *Lactobacillus plantarum*, *Bacillus subtilis*, *Rhizopus* spp., and *Mucor* spp., etc.) are inoculated naturally or artificially for ventilated koji making and takes 3–15 days. In the post-fermentation, where the addition of salt or brine and other spices is carried out and then fermented naturally [22,26]. Under the action of microorganisms, macromolecular substances in raw materials are hydrolyzed into small molecules of peptides, amino acids, sugars, and a variety of volatile flavor substances and functional nutrients (flavonoids, phenolic acids, and saponins) are produced at the same time [12,15,27,28]. Understanding the complex fermentation process of FSP, revealing the diversity of microorganisms, and analyzing the relationship between the core functional microorganisms and the related metabolites by combining molecular biology techniques and bioinformatics analysis tools in the fermentation process are conducive to regulate directionally the traditional fermentation process to enrich the formation of FSP-derived bioactive compounds.

Nation	Typical traditional fermented soybean products
China	Sufu, douchi, dajang, soybean sauce
Korea	Chongkukjang, Doenjang, meju,
Japan	Natto, Miso, soybean sauce
Indonesia	Tempeh
India	Hawaijar
Thailand	Thus nao

Province	Typical traditional fermented soybean products
Heilongjiang	Dajiang, sufu
Jilin	Dajiang, sufu, soy sauce
Liaoning	Dajiang
Beijing	Sufu
Shanxi	Sufu
Henan	Sufu, soy sauce
Hubei	Sufu
Chongqing	Sufu, douchi, soy sauce
Sichuan	Sufu, douchi, soy sauce
Yunan	Douchi, soy sauce, sufu
Guizhou	Douchi, sufu
Hunan	Douchi, sufu, dajiang
Guangxi	Douchi, sufu
Guangdong	Douchi, sufu, dajiang, soy sauce
Fujiang	Sufu, soy sauce
Taiwan	Douchi, sufu
Jiangxi	Douchi, sufu, soy sauce
Zhejiang	Sufu, soy sauce
Shanghai	Sufu, soy sauce
Anhui	Sufu
Jiangsu	Sufu

Figure 1. Geographical distribution and variety of traditional fermented soybean products in Asia countries.

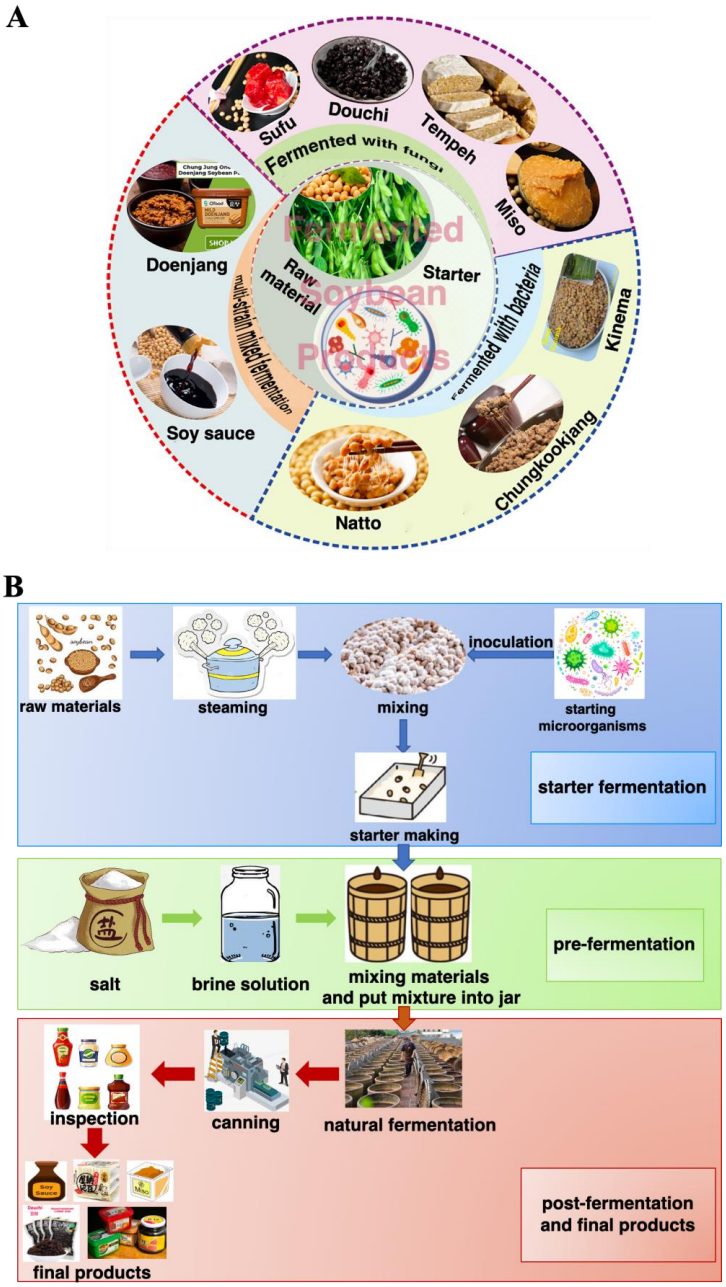


Figure 2. Fermented soybean products (**A**) and their production process (**B**).

3. T2DM and Its Pathogenesis

A widely acknowledged concept for T2DM is a heterogeneous and polygenic disorder resulting from genetic susceptibility, characterized by damaged insulin signaling, or insulin resistance, and a relative insulin deficiency of non-autoimmune etiology, and environmental elements involving overeating, obesity, stress, lack of exercise, and aging [29]. T2DM places considerable socioeconomic pressures on the individual and overwhelming costs to global health economies, estimated at US $825 billion [30].

Epidemiology of T2DM is affected by genetic and environmental factors. Genetic factors exert their effect following exposure to an obesogenic environment characterized by sedentary behavior and excessive sugar and fat consumption [31]. Under normal physiological circumstances, insulin controls blood glucose homeostasis within a narrow range via stimulation of glucose uptake into peripheral tissues mainly skeletal muscle as well as fat tissue through inhibiting the release of stored lipids from adipose tissue by liver. In T2DM, this mechanism is halted when insulin secretion is impaired via a dysfunction

of the pancreatic β-cell, and compromised insulin action because of insulin resistance, therefore resulting in multiple metabolic abnormalities [32]. Obesity and physical inactivity lead to insulin resistance, which together with a genetic predisposition, places stress on β-cells, leading to a failure of β-cell function and a progressive decline in insulin secretion [2]. It is well known that insulin resistance, a malfunctioning status when the insulin cannot play its biological effects but should be functional under the normal case, is the major contributor to the pathogenesis of T2DM. Muscle and liver, the two tissues responsible for the majority of glucose disposal following carbohydrate ingestion, are common tissues in which insulin resistance occurs; it also occurs in adipose, kidney, gastrointestinal tract, vasculature, and brain tissues, and pancreatic β-cells [2,29]. The intransigency of insulin action leads to impaired glycogen synthesis and glucose uptake in peripheral tissues [33].

Therefore, the most effective therapeutic strategies for patients with T2DM should target both aspects of the complex interaction between the target organs or tissues and the signaling pathways, thereby improving the glucose metabolism disorder.

4. Major Targets and Related Signaling Pathways of Glucose Metabolism and Homeostasis

Disrupted tissue glucose metabolism and systemic glucose homeostasis are important clinical features of T2DM [34]. Effective T2DM management requires a comprehensive approach to reduce blood glucose, normalize β-cell functions, and improve insulin sensitivity through weight management, diet, or medication [35]. This is not a simple task, given the complexity of the physiology of glucose homeostasis and the multifactorial nature of the metabolic syndrome. Organ systems involved in the regulation of glucose metabolism include the following: (1) The gastrointestinal tract, which processes dietary carbohydrates via α-amylase and α-glucosidase into glucose, and then delivers glucose to the systemic circulation and secretes incretin hormones that help regulate glucose disposal. (2) The endocrine pancreatic system, which regulates the expression of key glucoregulatory hormones such as insulin, glucagon, and amylin. (3) The hepatic system, where glucose production is initiated in the fasting state and glucose uptake is facilitated in the fed state. (4) Musculoskeletal and adipose tissue, where glucose is metabolized during energy expenditure or stored for future need [36]. The importance of the role of the gut in regulating glucose homeostasis has now also been highlighted, possibly by via alteration of the intestinal microbiota [37].

Within this complex network, nutrition plays a pivotal role on maintaining glucose homeostasis. Increasing evidence suggests that FSP can alleviate glucose metabolism disorders via the synergistic effect among the above-mentioned glucoregulatory organs [8,38–41]. The purpose of this review is to briefly summarize available data linking FSP to glucose metabolism disorders and to provide insights into their potential mechanisms of action via different glucoregulatory organs, which are highlighted in the sections below.

4.1. Effect of FSP on Carbohydrate Digestive Enzymes

One effective strategy to control postprandial hyperglycemia is to slow down the digestion of glucose through the inhibition of principal digestive enzymes such as α-amylase and α-glucosidase, which hydrolyze carbohydrates into absorbable monosaccharides [42]. Dietary carbohydrates are digested by α-amylase to smaller oligosaccharides, which are then further digested by α-glucosidase to glucose to be absorbed across the intestinal barrier aided by glucose transporters [43]. Inhibitors of α-amylase and α-glucosidase, which slow the final stages of carbohydrate digestion and consequently prevent the entry of glucose into the circulation, are considered a viable prophylactic treatment of hyperglycemia [44]. However, most classic drugs of α-amylase and α-glucosidase inhibitors (e.g., acarbose, voglibose and miglitol) have certain adverse effects such as flatulence, diarrhea, and abdominal pain [45]. Natural glucosidase inhibitors are identified from FSP (such as *douchi* in China, *doenjang* in Korea, *miso* in Japan, and *tempeh* in Indonesia, etc.) (Table 1). A previous study found that diabetic rats supplemented with 10% fermented soybean for 14 days

could reduce the α-amylase and intestinal α-glucosidase activities, which was due to the presence of phenolic phytochemicals [46].

Table 1. FSP inhibit carbohydrates digestive enzymes.

FSP	Origin	Functional Fractions or Components	Targets	Models/Methods	IC_{50} Value/Anti-α-Glucosidase Activities [a]	Main Results	Ref [c]
Douchi Hunan Sichuan Jiangxi	China	*Douchi* aqueous extract	α-glucosidase	Fluorescence	13.063 [a] 13.963 [a] 12.230 [a]	*douchi* samples from Hunan, Sichuan and Jiangxi province, respectively, showed a significantly higher anti-α-glucosidase activities than other samples ($p < 0.05$).	[47]
Douchi	China	*Douchi* aqueous extract	α-glucosidase	Fluorescence	6.85 [a]	The anti-α-glucosidase activity of *douchi* qu fermented with *Aspergillus oryzae* were higher than those of *Actinomucor elegans* and *Rhizopus arrhizus* and the highest anti-α-glucosidase activities were observed in *douchi* qu fermented with *A. orzyzae* at 5.0% and 7.5% salt levels.	[47]
Douchi	Japan	Water-soluble *douchi* extract	α-glucosidase	Normal male rats Diabetic patients	- [b]	*Douchi* extract inhibited α-glucosidase and efficiently regulated postprandial in rats and diabetic patients	[48]
Douchi	China	*Douchi* aqueous extract	α-glucosidase	L6 cells	0.35 mg/mL	Significantly improved glucose uptake in L6 cells	[41]
Doenjang	Korean	*Doenjang* aqueous extract	α-glucosidase	Fluorescence	27.40–40.98 mg/mL	*Doenjang* samples demonstrated considerable antioxidant, α-glucosidase inhibitory, and tyrosinase inhibitory effects	[49]
Doenjang	Korean	Brown rice fermented paste	α-glucosidase	High fat-fed mice	- [b]	Significantly inhibited the high fat-induced hyperglycemia	[50]
Doenjang	Korean	betaine	α-glucosidase	Fluorescence	- [b]	Inhibited α-glucosidase activity and pre-adipocyte differentiation	[51]
Kochujang	Korean	*p*-coumaric acid	α-glucosidase	Fluorescence	- [b]	Inhibited α-glucosidase activity and pre-adipocyte differentiation	[51]
Miso	Japan	miso	α-amylase and α-glucosidase	Fluorescence Human intervention trial	- [b]	Inhibited the activities of various digestive enzymes (α-amylase, α-glucosidase and trypsin) in vitro, and improved the postprandial blood sugar	[52]
Rice *miso*	Japan	Melanoidins	α-glucosidase	Fluorescence	- [b]	α-glucosidase inhibitory activity in rice *miso* were increased by prolonging the fermentation periods (3, 6, 24, 36 months)	[53]
Tempeh	Indonesia	Isoflavone	α-amylase and α-glucosidase	Fluorescence	74.8 mg/mL 85.3 mg/mL	Prevented diabetes due to the isoflavone (daidzein, genistein, and total isoflavone) in *tempeh*	[54]

[a] The IC_{50} is the concentration of the inhibitor producing a 50% inhibition. Anti-α-glucosidase activities of *douchi* samples were computed as the slope values from the curves of absorbance versus the concentration of aqueous *douchi* extract. The higher the slope value, the stronger the anti-α-glucosidase activity of the aqueous *douchi* extract. [b] "-" means not mentioned. [c] Ref: reference. FSP: fermented soybean products.

Douchi is a popular fermented soybean product with a history of use for over 2000 years. Many historical medical books have described *douchi* being able to prevent T2DM [22]. *Douchi* has attracted much attention as a functional food ingredient in recent years. Production of *douchi* is generally achieved by two processes: pre-fermentation (also called koji-making) and post-fermentation. Pre-fermentation could endow *douchi* with nutritional properties via the actions of different microbes. Post-fermentation is the key production process for developing the special nutrients and flavor of *douchi* and is carried out by adding salt and other spices to the koji, mixing, and leaving the mixture in a container [55]. Depending on the microbes that are present during the koji-making progress, *douchi* is usually classified into one of four categories: *Aspergillus*-type (i.e., Liuyang *douchi*), *Mucor*-type (i.e., Yongchuan *douchi*), *Rhizopus*-type (i.e., Indian *tempeh*), and *Bacterial*-type (i.e., Japanese *natto*).

Chen et al. [47] analyzed the α-glucosidase inhibitory activity of 31 *douchi* samples collected from various parts of China. Among them, samples from Hunan, Sichuan and Jiangxi province, respectively, showed a significantly higher anti-α-glucosidase activities than other samples ($p < 0.05$). The anti-α-glucosidase activity in *douchi* was associated with numerous factors, such as microorganisms, raw materials, additives, and fermentation parameters [16]. The anti-α-glucosidase activity of *douchi qu* fermented with *A. oryzae* was higher than those of *A. elegans* and *R. arrhizus*, which indicated that *A. oryzae* could utilize soybean to generate certain α-glucosidase inhibitor more effectively than *A. elegans* and *R. arrhizus* during the *douchi* fermentation [47], suggesting that the microbial species had different inhibitory activities on carbohydrate digestive enzymes during *douchi* fermentation. Furthermore, Fujita et al. [48] identified components in *douchi* with α-glucosidase inhibitory activity and found that *douchi* extract exhibited anti-glycemic activity via α-glucosidase inhibition action (IC_{50} = 0.34 g/L) in rats and humans. In their clinical trial of evaluating α-glucosidase inhibitory, the intake of *douchi* extract (0.3 g/meal, 3 times a day) for 6 months resulted in decreased blood glucose levels in 14 T2DM subjects (77.8%). Coincidentally, our group also found that the *Mucor*-type *douchi* extract could block the uptake of postprandial glucose by preventing the digestion of carbohydrates via α-glucosidase inhibition action (IC_{50} = 0.35 mg mL^{-1}) in L6 cells [41]. Moreover, we found that *douchi* extract-derived peptides Val-Tyr (VY) and Ser-Phe-Leu-Leu-Arg (SFLLR) with hypoglycemic activity in L6 cells [41].

Doenjang is a traditional food product through the fermentation of soybeans by naturally occurring bacteria (*Bacillus* species, in the early stage) and fungi (mainly *Aspergillus oryzae* and *Aspergillus niger*, in the later fermentation stage) and has been consumed for centuries as a rich protein source and flavoring ingredient in Korea [56]. Scientific reports reported that *doenjang* is a potent source of α-glucosidase inhibitor and could suppress postprandial hyperglycemia, making *doenjang* useful for treating diabetic and/or obese patients [49]. A study from Shukla et al. [49] found that *doenjang* samples demonstrated considerable α-glucosidase inhibitory effect in vitro and thus may hold the potential to reduce blood glucose responses to carbohydrate challenges. The α-glucosidase inhibitory activity of the starter culture of *doenjang* samples increases in a concentration-dependent manner and is also affected by the types and ratios of strains. Chun et al. [50] reported that the *doenjang* sample fermented with *A. oryzae*, *M. racemosus* 42, and *B. subtilis* TKSP 24 in a ratio of 1:1.5:0.5 showed the highest α-glucosidase inhibitory activity (67.14% ± 1.14%), indicating the potential applications of *doenjang* for treatment of T2DM. These findings confirm that the starter culture in *doenjang* has a significant effect on the α-glucosidase inhibitory activity. As reported previously, methanol extract of traditional *doenjang* from Jeju (Korea) displayed α-glucosidase inhibitory activities in the range of 33.5–44.3% [57]. Further, Yang et al. used metabolomic analysis to find that *doenjang* component responsible for inhibiting the α-glucosidase activities is betaine (a zwitterionic quaternary ammonium compound that is also known as trimethylglycine, glycine betaine, lycine, and oxyneurine), which suppressed carbohydrase activity by 72% by 10 mg/mL [51]. Interestingly, Shukla et al. [49] found that the content of polyphenols in *doenjang* also has a positive effect on the α-glucosidase inhibitory activity.

Miso is one of the fundamental seasonings used in Japanese cuisine made by the fermentation of soybean paste, which is said to have originated in ancient China or perhaps in Japan thousands of years ago. The use of *miso* spread among Japanese people during the Edo Period (1603–1868), and *miso* constitutes one of the hallmarks of the country's salted and fermented soybean seasoning along with *soy sauce* [58]. *Miso* is primarily made from soybeans, which are combined, fermented, and matured with soybeans and/or grains cultured with koji mold and salt [59]. This fermented product not only has a distinct mouthfeel and flavor but it is also demonstrated several health benefits, including anti-diabetes properties, improved digestion, and anti-hypertension [15]. Momose et al. [52] found that dietary intake of various kinds of *miso* could control postprandial blood sugar in a human intervention trial. Meanwhile, they found that all kinds of *miso* inhibited the activities of various digestive enzymes (α-amylase, α-glucosidase, and trypsin) to varied extents, which indicated *miso* may be a food that can be used to prevent diabetes in the future [52]. In another study, Jiang et al. [53] analyzed the α-glucosidase inhibitory activity of rice *miso* at different fermentation periods (3, 6, 24, 36 months). The results showed that α-glucosidase inhibitory activity in rice *miso* was increased at prolonged periods of fermentation. Furthermore, they concluded that melanoidins were the main α-glucosidase inhibitory activity component in rice *miso* [53].

Tempeh, a fermented soybean by *Rhizopus* spp. mold originally from Indonesia, is an excellent protein source with high nutritional quality [60]. *Tempeh* has higher nutritional values compared to soybeans because the fermentation process degrades carbohydrates, fat, and protein and improved their bioavailability. Astawan et al. reported that *tempeh* had a high α-amylase (IC_{50} = 74.8 mg/mL) and α-glucosidase inhibition values (IC_{50} = 85.3 mg/mL) [54]. *Tempeh* contains a higher content of isoflavones (daidzein, genistein, and total isoflavone) due to the action of microorganisms during the fermentation [54], and further study is needed to investigate the relationship between isoflavones and the activity of carbohydrate-cleaving enzymes.

4.2. Effect of FSP on Glucose Transporter-4 (GLUT4) Translocation and Glucose Utilization

Glucose homeostasis is maintained by a complicated and intertwined hormonal system that manipulates short-and long-term blood glucose regulation [61]. Insulin is crucial for maintaining plasma glucose homeostasis, via promoting glucose uptake from the circulation into the insulin-sensitive storage sites of muscle and adipose tissues by GLUT4 [62]. GLUT4 activation, i.e., translocation from intracellular storage sites to the cell membrane surface, is driven mainly through the activation of the insulin signaling cascade in adipose tissue and skeletal muscle, which facilitates glucose uptake [63]. Glucose can also be up-taken via GLUT2 in an insulin-independent manner in hepatocytes [64]. Studies have shown that in patients with T2DM, insulin resistance triggers lower expression and translocation of GLUT4. Therefore, increasing the levels and translocation of GLUT4 is a crucial factor in regulating glucose tolerance and insulin sensitivity to prevent the development of hyperglycemia [65].

Growing evidence has revealed that FSP can improve glucose utilization via GLUT4 activation (Table 2) [8,15,34,66]. Das et al. [67] examined the antidiabetic activity of popular fermented soybean foods in Northeast India. Results showed that among different traditional fermented soybean foods (*Akhuni*, *Bekang*, *Kinema*, *Hawaijar*, *Peruyaan*, and *Tungrymbai*) of Manipur, *Hawaijar* supplementation led to significant translocation of GLUT4 from the perinuclear region to the membrane in L6 myotubes in a dose-dependent manner from 1 to 5 mg/mL, resulting in increased glucose uptake. In another study, Huang et al. found that black soybean koji (a fermented black soybean product) treatment also increased the GLUT4 expression in a dose-dependent manner from 20 to 200 μg/mL in the insulin-resistant 3T3-L1 preadipocytes, thus promoting the glucose uptake [68]. Studies have found that *Hawaijar* extract could decrease fasting blood glucose, upregulate GLUT4 expression and glucose tolerance in the skeletal muscle tissues through phosphoinositide-3-kinase/protein kinase B/AMP-activated protein kinase (PI3K/AKT/AMPK) activation

with dose-dependent manner (50, 100, or 200 mg/kg BW/day for 16 weeks) after administration in HFD-fed rats [67]. A similar study also found that an extract from *Bacillus subtilis* MORI (BTD-1) fermented soybean could suppress adipocyte differentiation by inhibiting protein expression of the adipogenic gene, CCAAT/enhancer-binding protein-α (C/EBPα), but at the same time, it may also act as an agonistic ligand of peroxisome proliferator-activated receptor (PPAR)-γ, thereby increasing the GLUT4 translocation to the plasma membrane along with significantly increased glucose uptake into the adipocytes through improving insulin sensitivity [69]. However, there is a need to characterize the compounds that are responsible for promoting GLUT4 translocation. Huang et al. analyzed the content of isoflavone in the black bean koji but not for other flavonoids, such as anthocyanin, which are responsible for increasing GLUT4 expression [70]. The results revealed that fermentation caused the increase in the amount of isoflavone aglycones (daidzein and genistein) and a decrease in isoflavone glucosides (malonylgenistin and malonyldaidzin), indicating isoflavone-rich black bean koji may also have the similar functions against hyperglycemia [68]. Similarly, Kwon et al. [71] also found an increase in isoflavonoid aglycones (daidzein) and smaller peptides in *chungkookjang* extracts (a traditional Korean fermented soybean products with *Bacillus subtilis*) during fermentation, thereby enhancing glucose uptake resulted from stimulating translocation of the GLUT4 into the plasma membrane via activating insulin signaling and stimulates PPAR-γ activity in adipocytes. It's interesting to note that *douchi*-derived peptides (VY and SFLLR) could also increase GLUT4 translocation via the activation of AMPK and mitogen-activated protein kinase (MAPK) signaling pathways in L6 cells, leading to increased glucose uptake [41]. In another study, Das et al. found that a ~24 kDa single protein isolated (ISP) from HPI (*Hawaijar* protein isolate) could improve glucose utilization and insulin resistance, which was associated with GLUT4 translocation properties in the skeletal muscle tissues of high-fructose high-fat diet-fed rats [72]. ISP also showed insulin-sensitizing effects by facilitating insulin-dependent glucose uptake via GLUT4 translocation to the plasma membrane by inducing the PI3K/AKT cascade in C2C12 myoblast cells [72]. These results indicate that different compounds, responsible for GLUT4 translocation, are produced due to different microorganisms, raw materials, additives, and fermentation parameters in different fermented soybean products.

Table 2. Studies associated with hypoglycemia of FSP to prove GLUT4 expression and GLUT4 translocation.

FSP	Origin	Functional Fractions or Components	Targets	Models	Main Results	Ref [c]
BTD-1 [a]	Korea	- [b]	C/EBPα, PPAR-γ, GLUT4, ACC	3T3-L1 cells	Decreased expression of C/EBPα, increased the expression of GLUT4, ACC, and PPAR-γ, facilitated glucose uptake, suppressed the adipocytes differentiation	[69]
Black soybean koji	Taiwan	isoflavone aglycones (daidzein and genistein)	GLUT1, GLUT4, AKT, PPAR-γ, Acrp30	3T3-L1 cells	Increased GLUT1, GLUT4 and AKT protein expression, downregulated PPAR-γ level, upregulated Acrp30 protein expression, and improved glucose uptake	[68,70]
Chungkookjang	Korea	isoflavone aglycones (daidzein)	IRS-1, AKT, GLUT4, PPAR-γ	3T3-L1 cells	Increased IRS-1, AKT, and GLUT4 protein expression, stimulated PPAR-γ activity, enhanced glucose utilization	[71]
Douchi	China	Peptides VY and SFLLR	AKT, AMPK, p38 MAPK, p44/42 MAPK, GLUT4	L6 cells	Increased AKT, AMPK, p38 MAPK, p44/42 MAPK and GLUT4 protein expression, improved glucose uptake	[41]

Table 2. *Cont.*

FSP	Origin	Functional Fractions or Components	Targets	Models	Main Results	Ref [c]
Hawaijar	India	isoflavone	PI3K, AKT, AMPK, GLUT4, G6P	L6 myotubes High-fat diet-fed mice	Upregulated glucose uptake, G6P level, and AKT/AMPK/GLUT4 protein expression, reduced body weight, FBG, glycated hemoglobin, insulin resistance, and glucose intolerance	[67]
Hawaijar	India	~24 kDa protein	PI3K, AKT, AMPK, GLUT4, G6P	C2C12 cells High fructose high fat diet-fed animals	Upregulated glucose uptake, and PI3K/AKT/GLUT4 protein expression, reduced BW, FBG, IR, GHb levels, and glucose intolerance	[72]

[a] Soybean extract fermented by *Bacillus subtilis* MORI. [b] "-" means not mentioned. [c] Ref: reference. C/EBPα: CCAAT/enhancer-binding protein-α; PPAR-γ: peroxisome proliferator-activated receptor (PPAR)-γ; ACC: acetyl-CoA carboxylase; Arcp30: adipocyte complement-related protein of 30 kDa; AKT: protein kinase B; PI3K: phosphoinositide-3-kinase; IRS-1: insulin receptor substrate 1; AMPK: AMP-activated protein kinase; MAPK: mitogen-activated protein kinase; GLUT4: glucose transporter-4; G6P: glucose-6-phosphate; FBG: fasting blood glucose; BW: body weight; IR: insulin resistance; GHb: glycosylated hemoglobin; VY: Val-Tyr; SFLLR: Ser-Phe-Leu-Leu-Arg; FSP: fermented soybean products.

4.3. Effect of FSP on Muscle Glucose Homeostasis

Skeletal muscles represent the major site in maintaining normal glucose homeostasis and in regulating whole-body glucose metabolism [73]. The beneficial effect of FSP supplementation has been clearly implicated in the amelioration of impaired muscle glucose metabolism. Some studies demonstrated that FSP, such as *douchi* [41], *Hawaijar* [67,72], *chungkukjang* (a traditional Korean soybean paste fermented for only a few days) [74], and fermented soybean paste [75], could mimic the effect of insulin on glucose transport and glycogen synthesis through insulin-dependent and -independent signaling pathways in muscle tissues in vitro or in vivo. Therefore, FSP may have a direct role in affecting insulin sensitivity, glucose uptake, and utilization, and glycogen synthesis in muscle (Table 3).

Table 3. The mechanisms of modulating the effect of FSP on glucose homeostasis in muscle tissues.

FSP	Model	Target	Treatment	Effects	Ref [b]
Douchi	L6 myotubes cells	Skeletal muscle	100 μM VY/SFLLR	• Upregulation of GLUT4-mediated glucose uptake via the activation of AMPK and MAPK pathways	[41]
Hawaijar	C2C12 myotubes cells High-fat diet-fed mice	Skeletal muscle	2.5, 5, and 10 mg/mL in C2C12 cells 100 mg/kg BW/d for 16 weeks	• Increase in glucose uptake as a result of elevated of p-PI3K, p-AKT, and GLUT4 protein expression in C2C12 cells • Reduced BW, FBG, IR, and GHb levels • Increased p-PI3K, p-AKT, and GLUT4 protein expression in the skeletal muscle tissue	[72]
Chungkookjang	90% pancreatectomized diabetic rats	Skeletal muscle	40% fat diet with *Chungkookjang* for 8 weeks	• Increase the whole body of glucose disposal rates and glucose uptake into skeletal muscles	[74]

Table 3. *Cont.*

FSP	Model	Target	Treatment	Effects	Ref [b]
Fermented soybean paste	High-fat diet-induced obese mice	Skeletal muscle	100 mg/kg BW/d for 14 weeks	• Improvement of glucose tolerance and increased adiponectin levels concomitantly with enhanced AMPK activation in skeletal muscle • Suppressed the expression of pro-inflammatory cytokines in skeletal muscle.	[75]
Fermented soy permeate	STZ-induced diabetic rats	Skeletal muscle	FSP dose equivalent to 1 mg of soy isoflavones and 70 mg of alpha-galactooligosaccharides/kg of BW for 3 weeks.	• Stimulation of the conversion of intramuscular glucose into glycogen; leading to an accumulation of glucose in the muscle	[76]
FMCE [a]	C2C12 cells	Skeletal muscle	50–400 μg/mL in C2C12 cells	• Stimulation of glucose uptake via the activation of the AMPK pathway	[77]

[a] FMCE: fermented *M. citrifolia* 70% ethanolic extract. [b] Ref: reference. AKT: protein kinase B; PI3K: phosphoinositide-3-kinase; AMPK: AMP-activated protein kinase; MAPK: mitogen-activated protein kinase; GLUT4: glucose transporter-4; FBG: fasting blood glucose; BW: body weight; IR: insulin resistance; GHb: glycosylated hemoglobin; VY: Val-Tyr; SFLLR: Ser-Phe-Leu-Leu-Arg; FSP: fermented soybean products.

Compared to unfermented soybeans, *chungkukjang* supplementation increased whole-body glucose disposal rates and glucose uptake into skeletal muscles of high-fat diet-induced pancreatectomized diabetic rats via enhancing insulin signaling [74]. This indicated that fermented soybeans mainly with *Bacillus subtilis* improved glucose utilization, in comparison to unfermented soybeans in diabetic rats. In a high-fructose high-fat diet-fed rat model of type 2 diabetes, both *Hawaijar* [72] and fermented soybean paste [75] stimulated glucose uptake into skeletal muscle via enhanced PI3K/AKT and AMPK activation. In another study, Malardé et al. found that three weeks of consumption of fermented soy permeate stimulated the conversion of intramuscular glucose into glycogen, leading to an accumulation of glucose in the muscle of STZ-diabetic mice [76]. In KK-Ay/TaJc1 mice (genetically obese type 2 diabetes), *Morinda citrifolia* (aka Noni) fermented by *cheonggukjang* (fast-fermented soybean paste, FMC) supplementation reduced blood glucose and improved insulin resistance. Furthermore, FMC extract supplementation stimulated glucose uptake via the stimulation of PPAR-γ and AMPK in C2C12 myotubes [77]. Further, studies found that the intake of FSP offers protection against glucose metabolism disorders in muscle, which is an effect of the fermentation resulting in elevated contents of active ingredients (i.e., isoflavones aglycones and peptides) and higher diversity and richness of microbes [41,71,74,75].

4.4. Effect of FSP on Hepatic Glucose Homeostasis

Liver is the major organ of glucose metabolism including the synthesis, storage, and redistribution of carbohydrates and is an important target organ for the action of insulin [78]. However, T2DM impairs liver function resulting in the loss of the direct effect of insulin to suppress hepatic glucose production and glycogenolysis in the liver, thus causing an increase in hepatic glucose production [79]. A plethora of literature investigated the prophylactic role of FSP against diabetes-induced impairment of hepatic glucose metabolism via various molecular mechanisms (Table 4) [8,38,40,50,74,80–83].

Table 4. The mechanisms of modulating the effect of FSP on glucose homeostasis in liver tissue.

FSP	Model	Target	Treatment	Effects	Ref [a]
Meju	90% pancreatectomized diabetic rats	Liver	10% *meju* for 8 weeks	• Decrease in the serum glucose levels and increase the serum insulin levels as a result of improved glucose tolerance • Increase the expression of p-AKT and p-AMPK and decreased the expression of PEPCK in the liver resulting in the suppression of hepatic glucose output and promotion of glucose infusion rates • Improved β-cell function	[80]
Chungkookjang	90% pancreatectomized diabetic rats	Liver	40% fat diet with *Chungkookjang* for 8 weeks	• Reduction in fasting plasma glucose level • Improvement of glucose tolerance and insulin sensitivity • Decrease in hepatic glucose output as a result of increased the expression of p-IRS2 and p-AKT and suppressed PEPCK expression	[74]
Chungkukjang	C57BL/KsJ-*db*/db mice	Liver	5% *Chungkukjang* for 6 weeks	• Increase in the food intake efficiency ratios and decrease the level of the blood glucose and GHb • Increase of glucokinase and decrease of G6Pase and PEPCK enzyme activity in hepatic tissue	[81]
Kochujang	90% pancreatectomized diabetic rats	Liver	5% *Kochujang* for 8 weeks	• Increase in body weight gain as a result of the increase of epididymal fat pads and serum leptin levels • Improvement of glucose tolerance as a result of elevated insulin sensitivity • Suppression of hepatic glucose output and promotion of glycogen storage as a result of elevated the expression of p-STAT3 and p-AMPK and decreased the expression of PEPCK • Suppression of hepatic triacylglycerol synthesis as a result of increased the expression of p-ACC	[39]
Douchi	KKAy mice	Liver	0.4% *douchi* extract for 8 weeks	• Reduction in FBG, liver weight, and serum insulin level • Improvement of hepatic function as a result of decreased the level of GPT and γ-GTP and significantly suppressed GOT level	[40,83]
Doenjang	High fat diet-fed C57BL/6N mice	Liver	10% *Doenjang* for 8 weeks	• Reduction in body weight gain, adipose tissue weight, and blood glucose level • Improvement of glycogenesis as a result of the enhanced activity of the GK enzyme and inhibition of the G6Pase and PEPCK activities in the liver • Improvement of oxidative stress as a result of increased the activities of SOD, GR, and PON enzymes in hepatic tissue	[50]

[a] Ref: reference. ACC: acetyl-CoA carboxylase; Arcp30: adipocyte complement-related protein of 30 kDa; AKT: protein kinase B; IRS2: insulin receptor substrate 2; AMPK: AMP-activated protein kinase; PEPCK: phosphoenolpyruvate carboxykinase; G6Pase: glucose-6-phosphatase; STAT3: signal transducer and activator of transcription (STAT)-3; GPT: glutamic-pyruvic transaminase; γ-GTP: γ-glutamyl transpeptidase; GOT: glutamic-oxaloacetic transaminase; GK: glucokinase; SOD: superoxide dismutase; GR: glutathione reductase; PON: paraoxonase; GHb: glycosylated hemoglobin; FBG: fasting blood glucose; FSP: fermented soybean products.

Several animal studies and a few human studies have evaluated the effects of fermented soybeans on glucose metabolism as reviewed previously [8,38,74,83]. Previous studies found that both *meju* (unsalted soybean fermented with *Bacillus subtilis* and *Aspergilus oryzae*) and *chungkukjang* supplementation not only improved glucose uptake but also inhibited hepatic glucose output via potentiating insulinotropic actions and alleviating hepatic insulin resistance in 90% pancreatectomized (Px) diabetic rats, a moderate and non-obese type 2 diabetic animal model [74,80]. Similarly, a study performed by Kwon et al. confirmed that *kochujang* (a Korean fermented red pepper plus *meju* and soybean paste) supplementation lowered hepatic glucose output and triglyceride levels and increased glycogen storage via the activation of AMPK signaling, leading to glucose homeostasis

in 90% pancreatectomized diabetic rats [39]. In another study, Kim et al. [81] found that *chungkukjang* supplementation increased hepatic glycogen content and improved insulin tolerance via reducing glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) activity in C57BL/KsJ-*db*/*db* mice. Therefore, *chungkukjang* improved diabetic symptoms in type 2 diabetic rats more than non-fermented soybeans, and this was related to increased isoflavonoid aglycones such as daidzein and genistein and small peptides [82]. It's worth noting that hepatic function also has a significant effect on hepatic glucose homeostasis. Studies showed that supplementation with 4% of *douchi* extract (DE) for 60 days and 0.3 g of DE for 3 months in KKAy diabetic animals and mild type 2 diabetic patients, respectively, decreased fasting and postprandial blood glucose levels via reduced indexes of hepatic functional disorders such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [40,83].

On the other hand, chronic hyperglycemia is strongly associated with hepatocellular oxidative stress leading to hepatic damage [34]. A recent study has shown that dietary supplementation of fermented paste made from soybean, brown rice, or brown rice in combination with rice bran or red ginseng marc improved hyperglycemia and oxidative stress via regulation of the oxidative stress and hepatic antioxidant enzymes activities in mice fed with high-fat diet [50]. In 2022, Hariyanto et al. found that supplementation of soybean residue fermented with *Rhizopus oligosporus* and *Lactiplantibacillus plantarum* in STZ-induced hyperglycemic mice, can improve the glucose homeostasis via increasing antioxidative capacity and reducing reactive oxygen species (ROS) level, which was mainly attributed to the augmented contents of isoflavone aglycones and γ-aminobutyric acid (GABA) [84].

4.5. Effect of FSP on Adipose Tissue Glucose Homeostasis

Adipose tissue is an organ with active endocrine function involved in the regulation of energy balance and glucose homeostasis via multiple metabolic signaling pathways targeting the brain, liver, skeletal muscle, pancreas, and other organs [85]. Chronic excess calorie intake and the inability to generate new fat cells (adipocytes) may cause ectopic fat deposition, resulting in peripheral insulin resistance, particularly in skeletal muscle [86]. It is reported that insulin action as well as the expression of various adipokines in adipose tissue are disrupted by diabetes-induced metabolic complications [34]. However, FSP supplementation has been shown to influence the function of adipose tissue in subjects with diabetes [8,87,88]. And FSP can elicit insulin-sensitizing action via inducing adipocyte differentiation (Table 5) [69,71]. Two key transcription factors in this process are the PPAR-γ and C/EBPα. PPAR-γ activates genes involved in adipocyte differentiation and fatty acid sequestration [89]. A previous study found that after fermentation, *chungkookjang* enhances glucose utilization via activating the IRS1-PI3K-Akt-GLUT4 signaling pathway and stimulates PPAR-γ activity in adipocytes [71].

Table 5. The mechanisms of modulating the effect of FSP on glucose homeostasis in adipose tissue.

FSP	Model	Target	Treatment	Effects	Ref [b]
Fermented soybean paste	High-fat diet-induced obese mice	Adipocytes	100 mg/kg BW/d for 14 weeks	• Decrease in adipose size and downregulate the expression of genes involved in fatty acid uptake (CD36 and LDLR) and lipolysis in adipose tissue	[75]
BTD-1 [a]	3T3-L1 cells	Adipocytes	10–100 μg/mL in 3T3-L1 cells	• Increase of glucose uptake concomitant with increased GLUT4 expression • Suppression of the differentiation of 3T3-L1 adipocytes as a result of decreased the expression of C/EBPα and increased the p-ACC protein expression	[69]

Table 5. *Cont.*

FSP	Model	Target	Treatment	Effects	Ref [b]
Chungkookjang	3T3-L1 cells	Adipocytes	50 μg/mL in 3T3-L1 cells	• Increase in glucose utilization as a result of upregulated p-IRS-1, p-AKT and GLUT4 protein expression • Stimulation of PPAR-γ activity in adipocytes	[71]
Kochujang	3T3-L1 cells	Adipocytes	100 μg/mL in 3T3-L1 cells	• Decrease in the size of adipocytes by 24% compared with the control as a result of elevated the lipolysis-related mRNA expression of HSL • Inhibition of adipogenesis as a result of downregulated the mRNA expression of SREBP-1c and PPAR-γ	[90]

[a] BTD-1: soy bean extract fermented by *Bacillus subtilis* MORI. [b] Ref: reference. BW: body weight; IRS-1: insulin receptor substrate 1; AKT: protein kinase B; GLUT4: glucose transporter-4; C/EBPα: CCAAT/enhancer-binding protein-α; PPAR-γ: peroxisome proliferator-activated receptor (PPAR)-γ; ACC: acetyl-CoA carboxylase; SREBP-1c: sterol regulatory element-binding protein-1c; LDLR: low-density lipoprotein receptor; HSL: hormone-sensitive lipase; FSP: fermented soybean products.

Besides in vitro evidence, studies in vivo also supported the stimulatory effect of FSP on adipocyte differentiation. For instance, high-fat diet-fed obese mice supplemented with fermented soybean pastes for a period of 14 weeks showed significant increase in adiponectin levels in mesenteric adipose tissue concomitantly with the improvement of hyperglycemic parameters including plasma insulin level [75]. Despite the well-documented beneficial effects of enhanced PPAR-γ expression and adipocyte differentiation on insulin sensitivity, inhibition of adipocyte differentiation has also shown beneficial outcomes in some studies [91]. When 3T3-L1 adipocytes were treated with *kochujang* extract, the lipid accumulation was decreased by inhibiting adipogenesis through down-regulation of SREBP-1c and PPAR-γ [90]. On the other hand, *doenjang* has also been reported to elicit similar action in mice fed a high-fat diet [92]. In 2015, Hwang et al. demonstrated that the administration of an extract from fermented soybean (by *Bacillus subtilis* MORI) significantly suppressed adipocyte differentiation by inhibiting the C/EBPα protein expression in 3T3-L1 murine preadipocytes. These events were concomitant with the upregulation of GLUT4 translocation followed by increased glucose uptake [69]. However, it should be noted that inhibition of adipocyte differentiation per se without affecting whole-body energy balance is not beneficial for adipose tissue health and function. Inhibition of adipocyte differentiation could possibly result in the generation of hypertrophied adipocytes with less buffering capacity for circulating fats, and hence redistribution of body fat into non-adipose peripheral tissues in physiological conditions [93]. This would eventually lead to the development of insulin resistance in these tissues.

4.6. Effect of FSP on Pancreatic Morphology and Function

Insulin and glucagon, synthesized by β- and α-cells, respectively, are key regulators of glucose homeostasis. The pathophysiology of T2DM is associated with pancreatic tissue damage and compromised islets function [94]. Therefore, repairing of pancreatic tissue/cells is considered as a useful strategy to combat insulin deficiency and impaired glucose homeostasis. Multiple studies postulated that FSP can potentially ameliorate the pancreatic damage and promote insulin secretion to minimize the hyperglycemic condition (Table 6).

Table 6. The mechanisms of modulating the effect of FSP on glucose homeostasis in pancreatic tissue.

FSP	Model	Target	Treatment	Effects	Ref [b]
Chungkukjang	C57BL/KsJ-*db*/db mice	Pancreas	5% *Chungkukjang* for 6 weeks	• Improvement of insulin deficiency as a result of enhanced the function of β-cell	[81]
Chungkookjang	90% pancreatectomized diabetic rats	Pancreas	40% *Chungkookjang* for 8 weeks	• Improvement of glucose tolerance as a result of attenuated insulin resistance • Increase in glucose infusion rates as a result of improved β-cell function • Increase in pancreatic β-cell mass as a result of enhanced proliferation and reduced apoptosis • Enhancement of insulin synthesis and hyperplasia of β-cells as a result of increased expression of IRS2 and PDX-1	[95]
BTD-1 [a]	*db*/*db* mice	Pancreas	500 mg/kg BW for 8 weeks	• Improvement of glucose tolerance as a result of decreased the level of FBG, postprandial 2 h blood glucose, and HbA1c and increased the plasma insulin levels • Improvement of pancreatic β-cells integrity as a result of enhanced pancreatic islet architecture and the immunofluorescent intensities of insulin	[96]
Tempeh	STZ-induced diabetic rats	Pancreas	200 mg/kg BW for 30 days	• Improvement of the insulitis of islet as a result of increased the expression of Ki-67 (a proliferation marker)	[97]

[a] BTD-1: soy bean extract fermented by *Bacillus subtilis* MORI. [b] Ref: reference. IRS2: insulin receptor substrate 2; PDX-1: pancreatic duodenal homeobox-1; FBG: fasting blood glucose; HbA1c: hemoglobin A1c; BW: body weight; FSP: fermented soybean products.

For instance, administration of *chungkukjang* in C57BL/KsJ-*db*/*db* mice was shown to improve β-cell exhaustion and insulin deficiency, thus leading to improve insulin resistance in peripheral tissue [81]. Kwon et al. also supported that supplementation with *chungkukjang* in 90% pancreatectomized diabetic rats exhibited the ameliorative potential of insulin secretion by increasing the number of β-cells. This effect did not observe in unfermented soybeans [95]. Similarity, after 8-week feeding of a soybean extract from fermented soybean by *Bacillus subtilis* MORI in *db*/*db* mice, the pancreatic islet architecture was preserved and the immunofluorescent intensities of insulin [96]. In these studies, it was showed that the strain *Bacillus subtilis* has an important role in the antidiabetic effects of the product due to its ability to produce hydrolyzing enzymes [88]. Consistent with these findings, the administration of *tempeh* could also prevent pancreatic β-cell damage in STZ-induced diabetic rat model. However, it was proven by insulitis degree on Langerhans islet of diabetic rats fed by *tempeh* was lower compared to Langerhans islet of diabetic rats fed by soybeans [97]. This indicates that soybean through its fermentation process was more protective on pancreatic diabetes than un-fermented soybean.

4.7. Effect of FSP on Glucose Homeostasis through Gut Microbiota

Hippocrates, credited with the famous lines "All disease begins in the gut" and "Let food be thy medicine," appeared to have a very progressive view of how the gastrointestinal (GI) tract could play a mediating role between food and human health [98]. Dietary habits have been associated with the rising prevalence of health conditions resultant from gut microbiota dysbiosis [99]. Western dietary habits are characterized by high in saturated fats, refined carbohydrates and salt. Evidence suggests that this diet shift the composition of gut microbiota from fewer beneficial bacteria (e.g., *Bifidobacteria*, *Lactobacillus*, *Bacteroidetes*) to

more of the harmful bacteria (e.g., *Firmicutes*, *Clostridium*) [100,101]. This dysbiosis is a key factor in the onset and development of glucose metabolism disorder and other metabolic diseases. Overall, the evidence suggests that microbial profiles could be regulated by dietary changes.

Fermented soybean foods are reported to improve gut microbiome via their own microbiome or through their constituents in the matrix [102]. Soka et al. observed that *tempeh* treatment significantly increased the abundance of *Bacteroides fragilis* and *Clostridium leptum*, and decreased the abundance of *Firmicutes* in healthy SD rats [103]. Jeong et al. observed that the relative abundance of *Bacillales*, *Lactobacillales*, and *Verrucomicrobiales* (*Akkermensia muciniphila*) was increased, while the relative abundance of *Enterobacteriales* was decreased in type 2 diabetic rats supplement with *chungkookjang* [104]. They also found that *chungkookjang* treatment improved mucin contents by increasing beneficial bacteria, including *Akkermensia*, *Bifidobacterium*, and *Lactobacillus*, and decreasing harmful bacteria, *Enterobacteriales*, and promoting intestinal villi and goblet cells in partially pancreatectomized non-obese diabetic rats [21]. Their results suggested that *chungkookjang* could modulate glucose homeostasis by stimulating mucin secretion to promote *Akkermensia* and *Lactobacillus* growth and inhibit *Enterobacteriales* growth to regulate the gut microbial composition. Huang et al. found that *tempeh* intake significantly increased the relative abundance of *Lactobacillus* but decreased *Bacteroides* at the genus level in STZ-induced T2DM rats. Further study demonstrated that the therapeutic effect of *tempeh* on modulating glucose homeostasis was closely associated with the modulation of gut microbiota and increased intestinal short-chain fatty acids release [105]. While animal study supports a key role of FSP consumption on gut microbiota (Table 7), human studies are warranted to determine whether FSP can modify composition and metabolic activity of the human intestinal microbiota.

Table 7. The mechanisms of modulating effect of FSP on glucose homeostasis through gut microbiota.

FSP	Model	Target	Treatment	Effects	Ref [a]
Tempeh	SD rats	Gut microbiota	10% *tempeh* for 28 days	• Increase in the relative abundance of *Bacteroidetes*, *Bacteroides fragilis*, *Firmicutes* and *Clostridium leptum*, and decrease in the ratio of *Firmicutes*/*Bacteroidetes* as a result of resistant carbohydrates	[103]
Chungkookjang	90% pancreatectomized diabetic rats	Gut microbiota	4.5% diet for 8 weeks	• Improvement of mucin content as a result of increased the relative abundance of beneficial bacteria (*Akkermansia*, *Bifidobacterium*, and *Lactobacillus*) and decreased the relative abundance of harmful bacteria (*Enterobacteriales*) • Improvement of intestinal villi and goblet cells • Improvement of glucose homeostasis as a result of stimulated mucin secretion to promote *Akkermansia* and *Lactobacillus* growth and inhibit *Enterobacteriales* growth	[21,104]
Tempeh	STZ-induced diabetic rats	Gut microbiota	40 mg/kg BW for 4 weeks	• Increase in acetic acid, propionic acid, butyric acid, and valeric acid levels • Increase in the relative abundance of *Lactobacillus* but decrease *Bacteroides* at the genus level • Improvement of serum glucose, abnormal carbohydrate metabolism and lipid level as a result of altered in the internal microbiota	[105]

[a] Ref: reference. BW: body weight; FSP: fermented soybean products.

5. Conclusions and Future Remarks

In addition to improving sensory and nutritional attributes, mounting evidence supports that FSP are beneficial for decreasing the risk of onset and progression of glucose metabolism disorder, insulin resistance and T2DM. This review summarizes research progress on the glucoregulatory properties of FSP and their underlying mechanisms of action. In addition, the responsible components of FSP and their acting on cellular targets, signaling pathways, and tissues for regulating glucose homeostasis are discussed. Thus, effect of FSP (raw materials, fermentation processing) on glucoregulatory activity, possible target tissues and related signaling pathways were presented (Figure 3).

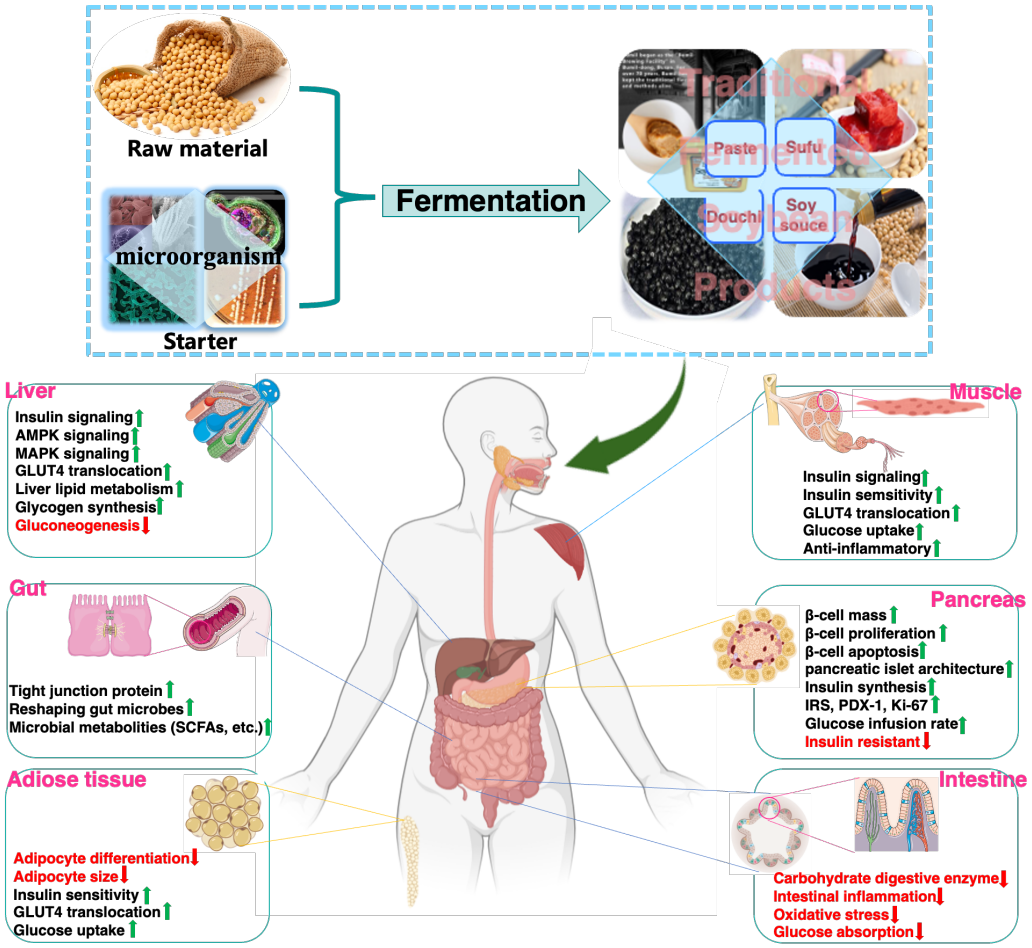
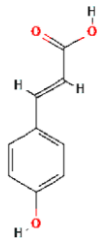
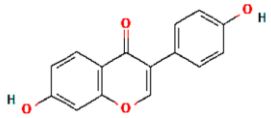
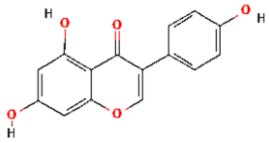
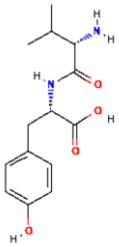
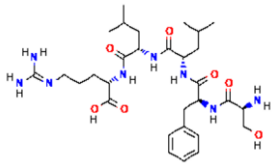
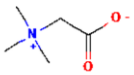


Figure 3. Glucoregulatory mechanisms of FSP on major organs.

A wide range of food bioactivity compounds, such as isoflavones, peptides, polyphenols, melanoidins, has been characterized as the responsible molecules for the glucoregulatory activity (Table 8). It should be noted that FSP such as *douchi*, *natto*, *tempeh*, *doenjang*, are whole foods that are also rich sources of dietary fiber; dietary fiber, including both soluble dietary and insoluble dietary fiber, is well established for their beneficial roles in improving glucose metabolism and insulin sensitivity [106,107]. However, the role of dietary fiber in FSP on glucose metabolism has not been studied. FSP contains numerous components, some presented naturally and some formed during fermentation, the effect of interactions of various components in FSP should not be overlooked. Animal studies in literature tend to use extracts from FSP, but not FSP, thus a possible synergistic effect with other food components might be compromised. Therefore, tremendous efforts are needed to reveal the synergistic effect of various components in FSP glucoregulatory activity [108].

Table 8. The responsible molecules for the glucoregulatory activity in FSP.

FSP [a]	Bioactive Compounds	Chemical Structures [b]	Ref [c]
Kochujang	*p*-coumaric acid		[54]
Tempeh	Daidzein		[60]
Tempeh	Genistein		[60]
Douchi	Val-Tyr		[41]
Douchi	Ser-Phe-Leu-Leu-Arg		[41]
Doenjang	Betaine		[54]

[a] FSP: fermented soybean products. [b] Chemical structures: the chemical structures of these bioactive compounds were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/, 1 march 2023), which is an open chemistry database at the National Institutes of Health (NIH). [c] Ref: reference.

Even though we have reviewed mechanisms of FSP action on glucoregulatory properties, given the complexity of the pathophysiology of glucose metabolism and the possible synergistic effect of various components in FSP, the nature of glucoregulatory mechanisms of FSP is far from understanding. Epidemiologic evidence supports the hypoglycemic role of FSP. However, clinical evidence on the hypoglycemic role of FSP is lacking, highlighting a critical need of translating research for bedside application.

Depending on the efficacy of dose, it is not known whether high-dose FSP intake might cause any adverse effects. Further, most of FSP generally contain high levels of NaCl. It's worth noting that high dietary salt is an important contributor to increased blood pressure and T2DM [109,110]. Salt reduction has been identified as one of the most cost-effective interventions for reducing the burden of cardiovascular disease and T2DM with the potential for saving millions of lives each year [111]. The sodium content should be reduced on the premise of ensuring the safety, quality, and functionality of FSP. Some strategies to reduce salt content in FSP include the application of non-thermal processing techniques such as high-pressure technology and ultrasound, the use of sodium salt alternatives, flavor enhancers, and/or quality improvers.

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