Benefit of Soybean-Derived Bioactive Peptides

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Peptides present in foods have a wide range of physiological functions, including as anticancer agents and in lowering blood pressure and serum cholesterol levels, enhancing immunity, and promoting calcium absorption. Soy protein can be partially hydrolyzed enzymatically to physiologically active soy (or soybean) peptides (SPs), which not only exert physiological functions but also help amino acid absorption in the body and reduce bitterness by hydrolyzing hydrophobic amino acids from the C- or N-terminus of soy proteins. They also possess significant gel-forming, emulsifying, and foaming abilities. SPs are expected to be able to prevent and treat atherosclerosis by inhibiting the reabsorption of bile acids in the digestive system, thereby reducing blood cholesterol, low-density lipoprotein, and fat levels.

Keywords: soybean ; bioactive peptide ; positive effect ; human health

1. Introduction

Soybeans contain lipids (20%), proteins (40%), carbohydrates (35%), and other substances (5%). The addition of 12–14% moisture is appropriate for stability during storage. The other substances consist of vitamins and minerals as minor components of the body. Recently, considerable attention has been given to soybeans as a functional food because they have been reported to contain phytochemical substances that prevent cancer and other chronic diseases [1]. Detailed studies of soybeans have identified at least 14 phytochemicals, such as carotenoids, coumarins, flavonoids, lignans, phytic acid, triterpenes, and phenolics, which are involved in cancer prevention [2]. Furthermore, protease inhibitors, oligosaccharides, and dietary fibers are also known to exhibit similar physiological functions [3]. Soybeans contain phytochemicals that possess anticancer, antiaging, antirenal failure, antiobesity, and anticholesterolemic activities. These phytochemicals can also inhibit HIV; prevent gallstone formation, senile dementia, and hyperlipidemia; promote diuretic action; suppress arteriosclerosis, provide relief from constipation; and prevent cardiovascular disease [4][5][6][7]. Therefore, soybeans are involved in the prevention of chronic diseases. Soybeans also contain substances that contribute to intestinal regulation, exert antioxidative properties, prevent osteoporosis, lower blood pressure, exert antithrombotic effects, boost immunity, and promote liver function [4][8][9].

2. Production of Soy Bioactive Peptide

Functional foods such as soybean-derived peptides (SPs) can prevent and treat certain diseases in addition to providing nutrition.

SPs are small protein fragments generated by in vitro enzymatic hydrolysis, fermentation (e.g., lactic acid bacteria-mediated fermentation), food processing (e.g., pH modification, heat treatment, protein isolation, ultra-high-pressure processing, and storage conditions) [10][11], and gastrointestinal digestion (specific and nonspecific proteases from the stomach, small intestine, and pancreas, including pepsin, trypsin, chymotrypsin, and pancreatin) of larger soybean proteins, which are beneficially associated with a multitude of metabolic activities [12][13]. The peptide composition is affected by enzymatic hydrolysis or bacteria-mediated fermentation and is also related to the type of soy protein [12]. SPs with different compositions have also been known to exhibit various functional properties with respect to quality, yield, and texture during tofu production [14]. Bioactive peptides comprising 2–20 amino acids are inactive when they are part of the parental protein sequence but become activated upon release by the methods described above [12][14][15].

3. Characteristics of Soybean Peptides

SPs may not seem very familiar, but they are quite common. For example, miso, soy sauce, and natto are examples of foods that contain fermented soybeans. These foods contain SPs in trace amounts [16].

SPs are substances produced during the process of protein degradation. Proteins in food are broken down into amino acids by digestive enzymes in the body while passing through the digestive tract and are absorbed into the small intestine.

However, at this time, all proteins are not completely degraded into amino acids and some are absorbed in the form of peptides in which several amino acids are bound [12].

SPs are hydrolyzed by combining soybean proteins with enzymes, and the resulting oligopeptides are composed of several amino acids. The physical characteristics of SPs include (1) high-concentration dissolution with low viscosity, (2) high clarity, and (3) low allergy compared with soy protein. In addition, purified SP has faster absorption into the body than amino acids [17][18].

4. Functionality of Soy Peptides

Soybean protein is a vital source of energy and contain essential amino acids for living organisms, including animals and especially humans, and has extensively studied [12]. Recently, there has been an increased interest in identifying bioactive peptides from natural sources such as plants. These peptides exhibit unique properties, such as antioxidative, antithrombotic, antimicrobial, immunoregulatory, opiate-like, mineral-binding, hypocholesterolemic, and antihypertensive effects because of their structure, composition, and amino acid sequence [12][19][20][21][22].

4.1. Neuroprotective Effects and Improvement of Cognitive Impairment

In spontaneously hypertensive rats (SHR) treated with the SP VHVV (10 mg/kg/oral administration) and ACE inhibitors (oral administered, 5 mg/kg) for 24 weeks, VHVV-treated animals were shown to have upregulated expressions of brain-derived neurotrophic factor (BDNF) related to long-term memory and neuronal survival [23]. These results suggest that VHVV may improve long-term memory and neurogenesis by activating cAMP response element-binding protein (CREB)-mediated downstream proteins as a molecular memory pathway.

SPs have also been reported to have positive effects such as cognitive function improvement, brain wave control, and neurotransmitter control in patients with mild cognitive impairment [24]. In a preclinical study using mice, SPs were shown to have a beneficial effect on age-related cognitive decline.

NWGPLV peptide with ACE inhibitory activity, identified from soy protein hydrolysate, decreased systolic blood pressure in a dose-dependent manner (~100 mg/kg) in an SHR model, leading to an antihypertensive effect [25]. Ovokinin (FRADHPFL) from ovalbumin induced vasorelaxation by attenuating bradykinin B1 receptor and prostacyclin as an endothelium-dependent relaxing factor. Ovokinin (2–7) (RADHPF) exhibited antihypertensive activity by regulating the expression of an unknown receptor and nitric oxide. Both peptides reduced blood pressure in the SHR model when administered orally at a dose of 10 mg/kg [26][27]. IFL and WL from tofu and fermented soybean were also shown to exhibit an ACE inhibitory activity [28]. The peptide HSYNLRQSQVSELKYEGNWGPLVNPESQQGSPRV, produced from soy milk during *Lactobacillus plantarum* C2-mediated fermentation, exerted ACE inhibitory and antioxidant activity [29]. LLPVFK, RLPKPW [30], and PGTAVPK [31] from soybean protein were shown to be associated with antihypertensive effects. It is necessary to further develop technologies that retain or enhance the activity of bioactive peptides in soybean foods. Moreover, it is important to understand the pharmacology of these peptides during their passage through the gastrointestinal tract without causing negative effects.

4.3. Inhibition of Chronic Kidney Disease Progression

Ingesting fermented soybean and lactic acid together can considerably delay the progression of chronic kidney disease (CKD) [32]. In a meta-analysis of patients with CKD, bean-based products were shown to greatly decrease the level of proteinuria and blood creatinine, inter alia, despite a lower increase in the glomerular filtration rate [33]. As lactic acid affects energy control and anti-inflammatory effects, when used together, it may prevent the release of cytokines, which is one of the main pathological features of CKD that leads to an inflammatory reaction and contributes to kidney damage. Therefore, the appropriate use of lactic acid may serve as an effective strategy for the treatment of kidney disease. Adenine, which is known to induce renal failure, was injected into female rats intraperitoneally to induce CKD. This was followed by the ingestion of fermented soybean together with lactic acid. In the rats with induced CKD, there was an expansion of the renal tubules and interstitial inflammation, as well as a substantial decrease in body weight and food intake. The group that ingested fermented soybean and lactic acid exhibited reduced expression of inflammatory markers, such as interferon gamma (IFN-γ), interleukin 1 (IL-1), IL-6, tumor necrosis factor-alpha (TNF-α), and Toll-like receptor 4 (TLR4).

4.4. Immunoregulatory Effects

Some immunostimulating peptides have been isolated from enzymatic digests of soybean proteins. These peptides contain specific binding sites on human blood phagocytic cells and stimulate phagocytosis in human and murine macrophages [34]. A tridecapeptide (MITLAIPVNKPGR; also known as soymetide-13) was demonstrated to stimulate phagocytosis of human neutrophils and promote TNF-α expression in mice [34]. An immunostimulating Q (Gln)-abundant peptide was isolated and purified from a soybean-based protein fraction digested with *Rhizopus oryzae*-derived peptidase R. The purified peptide, which was predicted to be located at or near the Q-rich region between residues 202 and 222 of the glycinin G4 subunit, increased the number of CD8(+), CD11b(+), and CD49b(+) cells in C3H/HeN mouse spleen cell cultures.

4.5. Inhibition of Cancer Cell Proliferation by SPs

The ingestion of various anticancer compounds present in soybeans suppresses breast cancer cell proliferation, and certain combinations yield synergistic effects [35]. A total of 12 bioactive factors (seven types reported from the soybean, viz., isoflavone, lunasin, lectin, trypsin inhibitors, saponin, and β-sitosterol) have been assessed for their antiproliferative activities against human breast cancer cells such as MCF-7 and MDA-MB-231. Of these compounds, those that exhibited strong activity were selected for further evaluation regarding whether they had a synergistic effect with bidirectional combination therapy in suppressing human breast cancer cell proliferation. Each compound enhanced the phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) by attenuating the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway, resulting in strong inhibition of benign tumor cell proliferation. The activation of AMPK led to suppression of tumor cell invasion and migration through regulation of the cell cycle and inhibition of protein synthesis, leading to anticancer effects. Synergistic effects that substantially increased AMPK phosphorylation were found between genistin and daidzein in MCF-7 cells and between genistein and β-sitosterol as well as between β-sitosterol and genistin in MDA-MB-231 cells. The combinations of these various bioactive factors in soybeans demonstrate a synergistic effect, which inhibits breast cancer cell proliferation [36].

4.6. Anti-Inflammation Properties

Because there are few studies on the autophagy and inflammatory effects of dietary peptides, the LPS-induced inflammation model (RAW 264.7) was used to study the effects of SPs as well as their underlying mechanism of action. The results showed that the SP QRPR decreased the levels of inflammatory cytokines (TNF-α and IL-6) induced by LPS in an inflammatory cell model. QRPR treatment resulted in a time-dependent activation of autophagy by the regulation of the PI3K/Akt/mTOR signaling pathway in LPS-treated RAW 264.7 cells (**Table 1**) [37]. These results show that QRPR attenuates the inflammatory response of cells by activating autophagy.

4.7. Modulation of Lipid Metabolism

SPs have shown effects on metabolic regulation and physiological properties, such as reduction of cholesterol and triglycerides levels, improvement of lipid metabolism, anti-obesity effects, inhibition of fatty acid (FA) synthase (FAS), and ant-diabetic effects [38]. Several molecules and processes have been the focus of the metabolic effects of bioactive peptides, including intestinal cholesterol micelles, cholesterol metabolism-associated genes that regulate cholesterol, triglyceride metabolism-related genes that reduce triglyceride levels, anti-obesity, dipeptidyl peptidase-IV (DPP-IV), α-amylase, α-glucosidase, and glucose metabolism-related genes that reduce blood glucose levels [38].

Soybean-derived soystatin (VAWWMY) inhibits the micellar solubility of cholesterol in vitro and cholesterol absorption in vivo, thereby playing an important in bile acid-binding activity [19][39]. In addition, β-lactoglobulin-derived lactostatin (IIAEK) reduces cholesterol levels by modulating the regulatory calcium-channel-related MAPK signaling pathway associated with cholesterol degradation [40]. These activities associated with lactostatin indicate that the extracellular signal-regulated kinase (ERK) pathway and calcium channels are involved in the activity of cholesterol 7α-hydroxylase (CYP7A1), a limiting enzyme for cholesterol degradation and transactivation induced by lactostatin in HepG2 cells (**Figure 1**) [40].

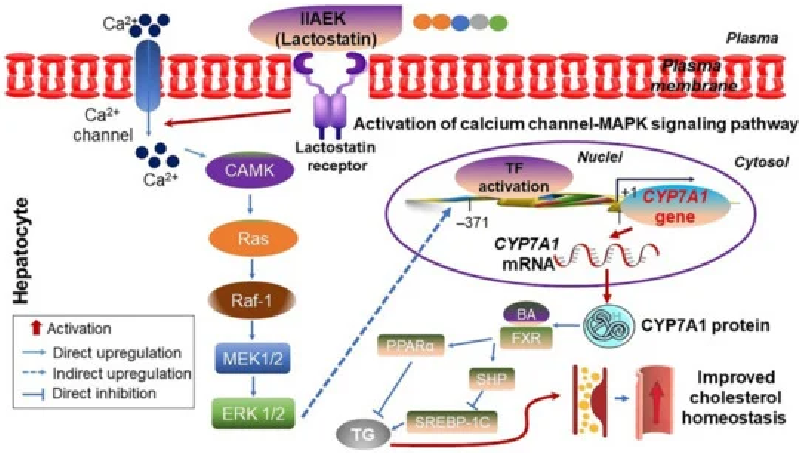

Figure 1. Proposed action mechanism of cholesterol degradation through lactostatin (IIAEK)-mediated *CYP7A1* gene expression in HepG2 cells. Lactostatin improves cellular calcium (Ca^{2+}) homeostasis via calcium channel. Subsequently, calcium ions activate calmodulin kinase (CAMK), small GTPase protein (RAS), proto-oncogene serine/threonine-protein kinase (Raf-1), mitogen-activated protein kinase kinase 1 and 2 (MEK1/2), and extracellular signal-regulated protein kinase 1 and 2 (ERK1/2). Upregulated ERK1/2 increases the expression of *CYP7A1* gene associated with cytochrome P450 monooxygenase at the mRNA and protein levels in hepatocytes, which leads to cholesterol homeostasis by regulating the expression of the gene associated with bile acid (BA), famesoid X receptor (FXR)/small heterodimer partner, peroxisome proliferator-activated receptor alpha (PPAR)-α, and sterol regulatory element-binding protein 1C (SREBP-1C). This figure is adapted from Kim et al. [4].

4.8. Antiobesity Effects

The dietary intake of soybean βCG reduces serum TG levels and visceral fat in hyperlipidemic humans [41] and exerts anti-obesity effects by promoting postprandial circulating levels of fibroblast growth factor 21 (FGF21) in mice [42]. By analyzing soy protein isolate (SPI) hydrolysates using LC-MS/MS, three lipolysis-stimulating peptides (ILL, LLL, and VHVV) that enhance lipolysis-stimulating effects regardless of gastrointestinal protease activity, which can act as potential anti-obesity agents, were identified (**Table 1**) [43].

The consumption of soy protein hydrolysate, a peptide mixture containing approximately 80% peptides with a molecular weight of ≤ 500 Da, reduced hepatic TG levels in the Otsuka Long-Evans Tokushima (OLETF) rat model. Moreover, an SP fraction containing KA, VK, and SY inhibited TG synthesis in HepG2 cells, although the in vitro mechanism of action remains unknown. Additionally, the dipeptide SY suppressed ApoB secretion in HepG2 cells (**Table 1**) [44]. These results suggest that soy protein hydrolysates containing bioactive peptides can reduce serum TG levels.

4.9. Antiarteriosclerosis Effects

The antiatherogenic activity toward blood vessels is another important property of soybean-based bioactive peptides. Apolipoprotein A-I (ApoA-I) is a major component of HDL. Several studies have investigated synthesized ApoA-I mimetic peptides. For example, 4F (DWFKAFYDKVAEKFKEAF) is a mimetic peptide of ApoA-I that was shown to exhibit antiatherogenic, anti-inflammatory, and antioxidative activity and enhance vascular repair in vitro in a rat model of scleroderma [45]. With regard to the antiatherogenic activity, 4F increased HDL formation and cholesterol efflux and decreased lipoprotein oxidation in vitro [45]. It also reduced renal inflammation in LDLR-null mice fed a Western diet; reduced arthritis in a rat model; decreased adiposity, increased adiponectin levels, and improved insulin sensitivity in obese mice; and enhanced HDL inflammatory activities in humans with coronary heart disease [45].

4.10. Antidiabetic Effects

Type 2 diabetes (T2D) results from insulin resistance or low insulin production in which the maintenance of glucose homeostasis is dysregulated. There has been considerable interest in natural remedies, such as food constituents, for the management of T2D. DPP-IV, α-amylase, and α-glucosidase are key enzymes that are directly associated with the regulation of blood glucose levels. Bioactive peptides that inhibit the activities of these enzymes may be effective for the control of T2D [46][38]. Because DPP-IV, an enzyme found both in the blood and in the cell membrane, is responsible for the inactivation of incretin hormones, glucagon-like peptide-1 and gastric inhibitory polypeptide, recent studies have focused on food-derived peptides as novel inhibitors [46][38]. DPP-IV inhibitory peptide (IAVPTGVA), identified in soybean-derived protein, may be used for the effective management of T2D and other metabolic diseases [46].

4.11. Skin Protection Effect of Soybean Oligopeptides against Ultraviolet Radiation

A research team conducted clinical and cellular studies [47] on the protective effect and mechanism of action of soybean oligopeptides against acute light damage to the skin induced by ultraviolet B (UVB) radiation. In a clinical trial, the skin erythema index in the UVB-irradiated group was significantly increased compared with that in the negative control group; however, the erythema index was significantly decreased in the group treated with soybean oligopeptides after UVB irradiation compared with that in the UVB group. In addition, on the 1st and 3rd days following UVB irradiation, skin stratum corneum hydration was significantly reduced compared with that in the negative control, but it was confirmed that soybean oligopeptides inhibited moisture loss due to UVB radiation.

4.12. Antioxidative Properties

The effect of SPs has rarely been studied in patients with hypertension. Black SPs have been shown to possess antioxidative properties. Following eight weeks of black SP dietary supplementation (4.5 g/d) in patients with hypertension, black SP improved redox homeostasis, including a decrease in plasma malondialdehyde (MDA) and urinary 8-epi-prostaglandin $F_{2\alpha}$ levels and an increase in plasma superoxide dismutase (SOD) activity. Furthermore, systolic blood pressure changes were negatively correlated with the change in serum total nitric oxide (NO) level. Elevated serum NO level was negatively correlated with serum ACE activity and MDA level was positively correlated with enhanced SOD activity [48]. The ACE-inhibitory peptide HHL, derived from a Korean fermented soybean product, exhibited antihypertensive activity in vivo [49].

4.13. Soybean Proteins and Control of Increased Gut Microbial Activity Caused by Probiotics

Based on the type of dietary protein, it is possible to control the effects of probiotics on gut fermentation. Although the use of common and widely known probiotics, such as dietary fiber and olive oil by gut microorganisms, results in the influx of 4–10 g of undigested protein, it was determined that mixing certain proteins can impact the fermentation process. Soybean protein, meat (beef + pork) protein, and fish protein were mixed with probiotics (cellulose or raffinose) and fed to rats for four weeks, and the resulting metabolic processes were analyzed. Rats that consumed raffinose as the probiotic instead of cellulose had an increased number of *Lactobacillus* spp., regardless of the type of protein. Compared with rats that ingested other animal-based protein combinations, rats that ingested soybean protein had an increased abundance of *Bifidobacterium* spp., comparable to the amount in the culture medium. This suggests that soybean protein supplied large amounts of nutrients for bacterial growth.

4.14. Antimicrobial and Antiviral Effects

Antimicrobial resistance is a significant concern in both the medical and food industry worldwide because microorganisms cause various diseases (e.g., inflammation-mediated diseases and food poisoning) [50]. The synthesized SPs PGTAVFK and IKAFKEATKVDKVVVLWTA have shown antimicrobial effects against *Pseudomonas aeruginosa* and *Listeria monocytogenes* above a dose of 625 μM and 37.2 μM, respectively [50]. The peptides KHPHGRSYKTKLRILA, LRFRAPAPVLRRIAKR, and HTSKALLDMLKRLGK, produced from *Bacillus subtilis* E20-fermented soybean meal, exhibit antimicrobial activity against *Vibrio alginolyticus* and *V*. *parahaemolyticus*, which could be a biofunctional source to prevent vibriosis in shrimp aquaculture [51].

A P13 (ALPEEVIQHTFNLKSQ) peptide produced by *B*. *licheniformis* KN1G-mediated soybean fermentation contains the human ACE2 cell receptor-binding domain. The P13-human TLR4/myeloid differentiation factor (MDF2) complex is known for its critical role in the cytokine storm based on in silico analysis. These results suggest that ALPEEVIQHTFNLKSQ has greater potential to be applied as an antiviral agent and used as a prophylaxis agent against viral diseases, including coronavirus disease 2019 and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [52].

5. Economic Feasibility and Application of Soybean-Derived Bioactive Peptides

Soy protein isolate or soy-derived bioactive peptides provide the financial benefits of relatively stable supply and cost, which can effectively supplement the volatility of milk protein products. The prediction of cost and supply for SPs is much easier than that for milk protein products, which makes cost management easy and increases the profitability of products. High-quality SPs may be used as financial substitutes for casein, milk protein concentrate, skim milk powder, whole milk powder, and whey protein-derived peptide material [53][54].

The effects of SPs can easily be sensed, as these are substances with rapid absorption. Thus, research on SPs is directed toward ensuring consumer experience. SPs currently in market have diverse applications such as in sports drinks, meal replacements, diet meals, and health supplements. SP material market has recently been experiencing rapid global growth as consumers have become increasingly aware of the benefits of soy peptides, including its nutritional and physiological effects, effects on physical fatigue related to absorption rate and sports nutrition, and effect on psychological fatigue related to stress [12][55][56]. In particular, the main attraction of products containing SPs currently available in market is fatigue recovery. In contrast to amino acid products that are mostly marketed through concepts of muscle fatigue relief and increased muscle strength for sportsmen, SP products distinguish themselves through the concept of fatigue recovery [57].

6. Conclusions

Traditional fermented foods prepared from soybeans or various peptides derived from soybean hydrolysates may be used as functional food materials to enhance antitumor (e.g., lunasin), anti-inflammatory, cognitive function, skin protection, and antioxidant activities. Because studies on the bioregulatory functions of SPs are at a nascent stage, structural determination of the peptides, identification of the mechanism of action, and large-scale expression by microorganisms should be conducted. This will lead to the discovery of new SPs with various physiological activities that may be utilized in the development of various bioregulatory functional foods, contribute to the improvement of public health, and further development of the food and pharmaceutical-related industries. These findings of this study suggest that SPs are an important resource that have potential applications in the nutraceutical, bioactive material, and clinical medicine fields, as well as for cosmetic and health care products.

SPs are known to exert many physiologically activities that remain to be elucidated. The results of various experiments at the cell and animal levels have not yet been fully linked to the effects and efficacy of human experiments and have not been fully interpreted. To overcome these limitations, it is necessary to discover bioactive peptides that maintain biological safety and pH stability in the gastrointestinal tract using human-based experiments. Furthermore, studies on the mechanism of action of these peptides should be conducted in parallel.

Until recently, it was thought that soybean protein was broken down into peptides and then converted into amino acids and absorbed by the body. SPs, which have the potential to be absorbed into the body and exhibit various functions, have attracted research interest because of their potential applications in human health. In the future, additional physiologically activities will be revealed, and accordingly, the benefits of SPs to human health will be further expanded.

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