Chapter

Soybean and Other Legume Proteins Exhibit Beneficial Physiological Effects on Metabolic Syndrome and Inflammatory-Related Disorders

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Abstract

There is currently a trend in Western countries to increase the intake of plant proteins. In this chapter, the author explains that this is due to the beneficial physiological functions of plant proteins, based on the latest literature review and our own research results. Among plant proteins, soy protein has been reported to have many beneficial effects on the improvement and prevention of metabolic syndrome. This chapter outlines the excellent effects of soy protein on renal function [improvement of early symptoms of diabetic nephropathy], which is closely related to metabolic syndrome, and the effects of combining these effects as complementary medicine. In addition, recent findings about the anti-inflammatory and immune activation effects of soy protein as hydrolyzed peptides are outlined. A brief introduction of the recent results of other legume-derived proteins that have replaced soy proteins are also explained. By further deepening our understanding of the superior physiological functions of plant proteins, it is hoped that their use expands even further.

Keywords: soy protein, metabolic syndrome, chronic kidney disease, inflammatory disorder, pea protein, lupin protein, mung bean protein

1. Introduction

Protein is not only significant as an energy source, but also as a component of the body, such as muscle and connective tissue, and as a physiological function substance, such as enzymes, hormones, and immune antibodies.

On the other hand, the problem of food shortage (in particular, protein) due to global population growth is becoming increasingly serious. Because of the economic development of emerging countries, people who used to consume energy from "carbohydrates" such as bread and rice are now tending to consume "proteins" such as meat and seafood as a luxury item, and there are concerns about a shortage of protein supply on a global scale. Under these circumstances, the effective use of plant proteins as a protein source has been attracting attention. Plant proteins have been considered to be less adaptable to human tastes in terms of flavor and physical properties than animal proteins, but recent superior food processing technologies have led to the marketing of "delicious" plant protein foods that are at the same level as animal protein foods.

It has been reported that plant proteins, especially soy proteins, have beneficial functions to improve and prevent lifestyle-related diseases that cannot be overcome by animal proteins, which are currently prevalent all over the world. The US Food and Drug Administration [FDA] has approved the health claim for food labelling that the consumption of 25 g of soy protein per day reduces the risk of heart disease [1]. In Japan, the Consumer Affairs Agency [formerly the Ministry of Health, Labour and Welfare] has allowed the health labelling of soy protein as a food for specified health use "to people who are concerned about cholesterol levels" [FOSHU].

The beneficial physiological effects of soy protein are presumed to be due to anti-inflammatory properties. The anti-inflammatory effect of soy protein is enhanced by its processing into peptides. Indeed, it has been reported that soy peptides suppress muscle inflammation pain relief in rheumatoid arthritis and ameliorate inflammatory bowel disease.

Recently, it is being reported that not only soy proteins, but also some legume-derived proteins have excellent physiological effects that are similar to, or even absent from, soy proteins. In this chapter, the author 1] introduces the beneficial physiological effects of soy protein for MetS, CKD and inflammation; 2] reports that these effects acted complementarily when used in combination with drugs; and 3] suggests other legume-derived proteins as alternatives to soy protein as novel proteins from legumes with beneficial physiological functions.

By understanding these findings, it is hoped that plant proteins will be used more actively to contribute to the improvement of human health, as well as their value as protein nutrition, which is in short supply worldwide.

2. Soy protein and peptides

2.1 Soy protein for metabolic syndrome (MetS)

The concept of MetS has been proposed by several committees. The first formalized concept of MetS was proposed by a consultation group for the definition of diabetes for the World Health Organization (WHO); it was determined to have a high-risk status with multiple risk factors for cardiovascular disease. This group emphasized insulin resistance as the major underlying factor [2]. In 2001, a definition for MetS was devised by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) [3]. The American Heart Association and the National Heart Lung and Blood Institute updated this definition in 2005 [4]. This updated definition is one of the most widely used criteria for MetS. The International Diabetes Foundation (IDF) published new criteria for MetS [5] in 2005. Although it includes the same general criteria as the other definitions, it requires that obesity, but not necessarily insulin resistance, be present. Although visceral obesity is now recognized as an important factor, the IDF definition has been criticized for its emphasis on obesity, rather than insulin resistance, in pathophysiology [6].

In Japan, in 2006, MetS was defined as a multiple risk factor clustering syndrome caused by visceral fat accumulation and insulin resistance that accompanies this accumulation [7]. In the MetS stage, it is advocated that lifestyle intervention to reduce visceral adiposity should be given priority over drug treatment. Subjects with multiple risk factor syndrome were diagnosed with MetS if their visceral fat areas determined by CT scan were over 100 cm^2.

The Japanese Committee for the Definition and Diagnosis of MetS aimed to select subjects with multiple risk factors in which lifestyle modification to reduce visceral adiposity has priority over drug treatment [8]. For this purpose, the Japanese government started a new health policy that provides a specific health check-up followed by specific counseling for subjects diagnosed with MetS according to the Japanese criteria from 2008.

Title	Number of articles	Number of total subjects	Outcome [significant difference]	Reference
Meta-analysis of the effects of soy protein intake on serum lipids.	38	743	Total-C↓, LDL-C↓, TG↓	[9]
Meta-analysis of the effects of soy protein containing isoflavones on the lipid profiles.	23	1,381	Total-C↓, LDL-C↓, TG↓, HDL-C↑	[10]
A meta-analysis of the effect of soy protein supplementation on serum lipids.	41	1,756	Total-C↓, LDL-C↓, TG↓, HDL-C↑	[11]
Hypocholesterolaemic effects of soya proteins: result of recent studies are predictable from Anderson meta-analysis data.	27	923	Total-C↓, LDL-C↓	[12]
Soy protein effects on serum lipoproteins: a quality assessment and meta-analysis of randomized, controlled studies.	43	1,946	LDL-C↓, TG↓, HDL-C↑	[13]
Effect of Plant Protein on Blood Lipids: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.	112 (non-soy; 18)	5,774 (non-soy; 599)	LDL-C↓, Non-HDL-C↓, Apo-B↓	[14]
A Meta-Analysis of 46 Studies Identified by the FDA Demonstrates that Soy Protein Decreases Circulating LDL and Total Cholesterol Concentrations in Adults.	43	2,607	Total-C↓, LDL-C↓	[15]
The effects of isolated soy protein, isolated soy isoflavones and soy protein containing isoflavones on serum lipids in postmenopausal women: A systematic review and meta-analysis.	46		Total-C↓, LDL-C↓, TG↓, HDL-C↓, hypercholesterolemic subjects' Apo-A1↓	[16]

Note: ↓ and ↑ signs represent decrease and increase, respectively, after supplement of active compounds. Total-cholesterol (Total-C); low-density lipoprotein cholesterol (LDL-C); triglyceride (TG); high-density lipoprotein cholesterol (HDL-C); non-high-density lipoprotein cholesterol (non-HDL-C); apo-lipoprotein-B (Apo-B); apo-lipoprotein-AI (Apo-AI).

Table 1.
Meta-analysis on improving lipid metabolism in soy protein.

Soy protein exerts not only conventional nutritional value but also beneficial effects on human health. Many randomized controlled trials (RCTs) have assessed the effects of soy products on serum lipids. Systematic reviews and meta-analyses have reported improvements in lipid metabolism (**Table 1**) [9–16].

Soy protein isolate [SPI] is composed of three major components, glycinin [approx. 40%], β-conglycinin [approx. 20%], and lipophilic proteins (approx. 40%) [17]. Glycinin and β-conglycinin are storage proteins in soy, and lipophilic proteins consist primarily of membrane proteins. Among these components, β-conglycinin has the function of lowering serum triglycerides preferentially over serum cholesterol [18]. Digestive decomposition products of β-conglycinin were reported that lowering the activity of fatty acid synthase and increasing the activities of β-oxidation enzymes, and the fecal excretion of TG was high in β-conglycinin-fed mice and rats [19, 20]. Therefore, in the calculation based on the recommendation by the FDA, the same effect can be expected with 5 g of β-conglycinin. In clinical study, daily consumption of 5 g of β-conglycinin per subject significantly lowered serum TG concentrations, and the apo B and VLDL-TG concentrations were significantly decreased [21]. Hence, β-conglycinin consumption may specifically affect TG metabolism. In addition, the intake of 5 g of β-conglycinin per day decreased the body fat ratio and visceral fat [21, 22]. Additionally, serum adiponectin significantly increased with the consumption of β-conglycinin, and serum free fatty acids in the β-conglycinin group were significantly decreased. Tachibana et al. showed that β-conglycinin improves insulin sensitivity in rats [23]. β-conglycinin might be an important food component for the prevention and/or amelioration of visceral fat syndrome, which is also called MetS (**Table 2**) [21, 22, 24–27].

2.2 Soy protein for chronic kidney disease

Chronic kidney disease [CKD] is a major public health burden, with a global prevalence of ~11% in the general adult population [28]. If left untreated, CKD slowly progresses to end-stage renal disease, which requires dialysis or kidney transplant. Worldwide, a 31.7% increase in CKD mortality was observed over the last decade [29]. Effective interventions to prevent and delay the progression of CKD are well recognized. Prevention should start at the government level with the institution of multisectoral polices supporting sustainable development goals [SDGs] and ensuring safe and healthy environments.

CKD is bidirectionally associated with MetS and cardiovascular diseases [CVDs] [30, 31], and diabetic nephropathy [DN] is a complication of diabetes [32]. Moreover, it has been reported that 40% of patients undergoing dialysis are doing so because of DN [33], and approximately 50% of type II diabetes patients exhibit urinary albumin disease, which is an early stage of DN [34].

For CKD prevention, it is important to gain insight about commonly consumed foods and beverages in relation to kidney function. A report has been published in which PubMed was comprehensively searched for papers published until August 2019 describing prospective cohort studies and was supplemented by manual searches of reference lists from appropriate studies [35]. In this report, there was convincing evidence that a healthy dietary pattern may lower CKD risk. Red (processed) meat, poultry, fish, dairy, vegetables, legumes, nuts, and fruits were recommended foods for CKD patients. Dietary patterns were recommended adherence to the Dietary Approach to Stop Hypertension (DASH) diet, Mediterranean diet, and other healthy dietary patterns. As unhealthy diets, high-fat and high-sugar diets and high-acid-loaded diets were pointed out. In the Atherosclerosis Risk in Communities [ARIC] study of ~12,000 US participants with 23 years of follow-up,

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Study title	Design of study	Number of subjects	Duration of study	Dose of β-conglycinin	Outcome [significant difference]	Reference
Decrease in serum triacylglycerol and visceral fat mediated by dietary soybean β-conglycinin[*1].	Randomized, Double-Blind, Placebo-Controlled Study	Test1;138 Test2:102	Test1:12-wk Test2:20-wk[*1]	4.4 g/day	Test1; TG↓, Apo-B↓, VLDL-TG↓ Test2; Visceral fat↓	[21]
Effects of soybean beta-conglycinin on body fat ratio and serum lipid levels in healthy volunteers of female university students.	Randomized, single-blinded crossover design	41	8-wk	4.4 g/day	Body fat ratio↓	[22]
Serum triacylglycerol-lowering effect of soybean β-conglycinin in mildly hypertriacylglycerolemic individuals.	Randomized, Double-Blind, Placebo-Controlled Study	68	12-wk	2.3 g/day	TG↓, HDL-C↑, Apo C-II↓	[24]
Serum lipid-improving effect of soyabean β-conglycinin in hyperlipidaemic menopausal women.	Randomized, Double-Blind, Placebo-Controlled Study	100	12-wk	2.3 g/4.6 g	TG↓, LDL-C↓, Apo-B↓, NEFA↓	[25]
Improvement of Triglyceride Levels through the Intake of Enriched-β-Conglycinin Soybean (Nanahomare).	Randomized, Double-Blind, Placebo-Controlled Study	134	12-wk	38.8 g/week	TG↓	[26]
Effects of beta-conglycinin intake on circulating FGF21 levels and brown adipose tissue activity in Japanese young men.	Single-blinded randomized crossover trial	21	2-wk	9.2 g/day	FGF21↓, BAT act↑	[27]

*Note: *1; Test 1 is an examination of the serum triglyceride level and Test 2 is a measure of visceral fat by means of CT scanning. ↓ and ↑ signs represent decrease and increase, respectively, after supplement of β-conglycinin. Triglyceride (TG); apo-lipoprotein-B (Apo-B); very low-density lipoprotein triglyceride (VLDL-TG); high-density lipoprotein cholesterol (HDL-C); apo-lipoprotein-CII (Apo-CII); low-density lipoprotein cholesterol (LDL-C); non-esterified fatty acid (NEFA); fibroblast growth factor 21 (FGF21); brown adipo tissue activity (BAT act).*

Table 2.
Clinical studies for lipid metabolism improvements of β-conglycinin.

consumption of legumes was significantly associated with lower risks of CKD, with an HR of 0.83 [95% CI, 0.72; 0.95] for high versus low intakes [36]. Soy protein, which is representative of legumes, has been reported to suppress the progression of DN [37, 38]. The effects of soy protein on DN/CKD in clinical trials are summarized in **Table 3** [39–43].

Kidney disease patients are carefully monitored for protein intake, and restricted protein intake according to the progression of their condition by doctors and nutritionists. However, there are some reports showing that mild protein restriction does not suppress the progression of kidney disease [44–46]. Therefore, it is necessary to consider not only the quantity but also the quality of protein. Legumes, including soy protein, can be regarded as very significant proteins to help treat nephropathy.

Study title	Design of study	Number of subjects	Duration of study	Outcome [significant difference]	Reference
Soy protein intake, cardiorenal indices, and c-reactive protein in type 2 diabetes with nephropathy.	Longitudinal randomized clinical trial study	41	4-y	FPG↓, Total-C↓, LDL-C↓, TG↓, CRP↓, Proteinuria↓, Urinary creatinine↓	[39]
The effects of soy protein on chronic kidney disease: a meta-analysis of randomized controlled trials.	Meta-analysis [9 studies]	Total 197	6-wk~4-y	Serum creatinine↓, Phosphorus↓, TG↓	[40]
Soy-based renoprotection.	Single arm intervention (3 studies) Placebo-controlled chronic intervention [22 studies]	Total 634	4-wk~6-mo	Total-C↓, LDL-C↓, Urinary creatinine↓, [Urinary albumin↓]	[41]
Effects of soy protein containing isoflavones in patients with chronic kidney disease: A systematic review and meta-analysis.	Meta-analysis [12 studies]	Total 280		Serum creatine↓, Phosphorus↓, CRP↓, Proteinuria↓, BUN↓ [in predialysis subgroup]	[42]
Soy Protein and Chronic Kidney Disease: An Updated Review.	RCT (3 studies), DBRCT, CRCT, LRCT Total 6 studies	Total 335	1~24-wk	Urinary urea nitrogen↓, Proteinuria↓, Blood sodium↓, Serum Creatinine↓	[43]

Note: ↓ sign represents decrease, after supplement of soy protein. Fasting plasma glucose [FPG]; total-cholesterol (Total-C); low-density lipoprotein cholesterol (LDL-C); C-reactive protein [CRP], blood urea nitrogen (BUN).

Table 3.
Summary of clinical studies by soy protein for CKD.

2.3 Anti-inflammatory roles of soy protein and peptides

Inflammation can occur when infectious microorganisms such as bacteria, viruses, and fungi invade the body and circulate in the blood, and/or when they enter certain tissues [47, 48]. Inflammation can also occur during the course of pathologies such as tissue damage, cell death, cancer, ischemia, and degeneration [49–51].

There are reports of the anti-inflammatory effects of soy protein and its hydrolysate peptides [52]. Among them, lunasin is considered one of the most studied bioactive peptides. Since its discovery in soybean twenty years ago, many researchers around the world have focused their studies on demonstrating the chemo preventive and chemotherapeutic activity of lunasin [53–55]. Lunasin is a 44 amino acid peptide isolated from soy that has three domains implicated in anticancer activity: an RGD motif [Arg-Gly-Asp], a helical domain with a sequence conserved in chromatin binding proteins [Glu-Lys-His-Ile-Met-Glu-Lys-Ile], and a poly-aspartic acid tail [56]. Lunacin has been reported to have unique antioxidant, anti-inflammatory, and anti-cancer properties, and to play an important role in the regulation of cholesterol biosynthesis in the body [57]. Lunacin has potential as a dietary supplement by its high bioavailability and thermal stability.

Trypsin digests of soy proteins revealed that the sequence MITLAIPVNKPGR was able to stimulate phagocytosis in leukocytes. This peptide derived from β-conglycinin was named "Soymetide". The Met at its N-terminus was essential for its activity [58]. Four residues of the C-terminal residues of Soymetide-13 could be removed to form Soymetide-9 [MITLAIPVN], which had the highest activity. In these 9 residues [Soymetide-9], Soymetide-4 [MITL] is the minimal sequence required for its activity [58].

Soy protein with or without isoflavones was shown to reduce oxidative stress and have anti-inflammatory properties by inhibiting nuclear factor-kappa B [NF-κB] and blocking the secretion of pro-inflammatory cytokines in model rats and mouse. In clinical study by subjects with end-stage renal disease and healthy women over 70 years of age, their oxidative stress and inflammatory symptom were reduced [59]. The bioactive peptides RQRK and VIK were produced by digestion with pepsin and pancreatin from soy milk. These peptides inhibited lipopolysaccharide-induced inflammation in murine macrophages and the production of nitric oxide, interleukin [I])-1, nitric oxide synthase, and cyclooxygenase-2 [60].

Inflammatory bowel disease [IBD] is an intractable disease that causes inflammation of the gastrointestinal tract. Ulcerative colitis and Crohn's disease are the two major pathologies of IBD [61]. Ulcerative colitis is a non-specific inflammatory disorder that causes ulcers and erosion, primarily in the colonic mucosa. Young et al. revealed that soy peptides were effective in preventing dextran sulphate sodium[(DSS)-induced colitis in pigs [62]. The soy-derived tripeptide Val-Pro-Tyr [VPY] has been reported that anti-inflammatory effects in Caco-2 and THP-1 macrophages and inhibition of the secretion of IL-8 and TNF-α in a DSS-induced colitis model mouse [63]. They suggested that tripeptide VPY from soy peptides may be promising for the treatment of IBD.

Insulin resistance and diabetes has revealed to relate closely between nutrient excess and activation of the innate immune system in most organs pertinent to energy homeostasis by the research for a mechanism linking the pathogenesis of obesity over the past two decades [64–66]. Inflammation has been revealed to occur as a consequence of obesity, and to play a causative role in generating insulin resistance, defective insulin secretion [i.e., MetS), and disruption of other aspects of energy homeostasis by recent many studies. It has been reported that the suppressive effect of soy protein on the progression of CKD/DN, which is highly related to MetS, is also exerted by the anti-inflammatory effect in renal tubules [67]. From such a close relationship between MetS and inflammation, it is easy to predict that the beneficial effect of soy protein on MetS may be due to its anti-inflammatory effect.

3. Complementary effects of soy protein/peptide in combination with drugs

3.1 Effect of combined use with anti-hyperlipidaemic drugs

The mechanism by which soy protein lowers cholesterol differs from that of statins and fibrates. Soy protein lowers serum cholesterol levels by acting as a bile acid sequestrant, which binds bile in the gastrointestinal tract to prevent its reabsorption by performing the same anion exchange reaction as the resin cholestyramine [68, 69].

Statins and fibrates are drugs developed to improve blood lipid levels. Statins are known as the most efficient agents for reducing plasma cholesterol. Statins target hepatocytes and inhibit 3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase in cholesterol metabolism. Accordingly, statin and soy protein are expected to act additively or synergistically to decrease cholesterol levels. There are known serious side effects from statins, including muscle symptoms, rhabdomyolysis [secondary renal failure due to destruction of specific muscle tissue], peripheral neuropathy, myopathy, liver dysfunction, and thrombocytopenia [70–73]. Rhabdomyolysis often induces sudden kidney failure [74]. Fibrates, which are antagonists of peroxisome proliferator-activated receptor α [PPARα], are used in adjunct therapy for hypertriglyceridemia and are usually used in combination with statins. As fibrate-related side effects, the slight gastric region discomfort and myopathy [myalgia with increased creatinine phosphokinase] have been reported. In addition, increasing of the gallstones risk has been known by fibrates because of increasing of cholesterol in the bile duct. Use in combination of statins and fibrates is reported to even more raise the risk of rhabdomyolysis. So, combination use of these two agents is contraindicated in principle.

Nabiki et al. examined the effects of SPI on weight loss, markers of diabetes, and parameters of dyslipidaemia in obese diabetic patients by treated with statins and/or fibrates because of high levels of LDL cholesterol and triglycerides [75]. As a result, body weights of these patients decreased significantly by approximately 1 kg and their waist circumferences got thinner significantly by approximately 2 cm. Total cholesterol, triglyceride, LDL cholesterol, apolipoprotein B, and glycated hemoglobin levels of these patients decreased significantly, and HDL cholesterol levels increased significantly. In addition, a lipid metabolism-improving effect was also observed in patients who did not decrease weight. Therefore, it was suggested that the improving effect of lipid metabolism-related factors in these patients was not only due to weight loss but also a direct effect of soy protein. Use of soy protein may help to reduce the drug dose for dyslipidaemia. SPI is recommended for patients with mild dyslipidaemia prior to drug therapy or for maladaptive disease patients, such as those who have side effects from medications.

Combination prescription of fibrates and statins for patients with renal dysfunction and dyslipidaemia is contraindicated. Thus, physicians are unable to adequately treat lipid abnormalities for chronic kidney disease patients. It has been reported that when chronic kidney disease patients with dyslipidaemia ingested β-conglycinin, a major component of soy protein, for 3 months, triglyceride and LDL cholesterol levels improved. Renal function during the consumption period of β-conglycinin showed a tendency to improve despite protein intake [76]. β-conglycinin may help improve lipid abnormalities in patients with renal dysfunction as a complementary medical food material without decreasing kidney function. Moreover, β-conglycinin may improve renal dysfunction as a direct and/or secondary effect of ameliorating lipid abnormalities.

3.2 Concomitant effect with rheumatoid arthritis drug

Rheumatoid arthritis is due to inflammation triggered by an immune response to autoantigens. Many of these patients have swelling and pain due to polyarticular arthritis. Their pain interferes with activities of daily living [ADLs], such as cleaning, washing, dressing, and undressing. These patients are anxious for more comfortable ADLs with reduced pain. The mechanisms of onset of rheumatoid arthritis have been reported in many studies. Based on these results, numerous new therapeutic agents have been developed.

As a specific case of improved inflammation, outpatients with rheumatoid arthritis consumed soy peptide with therapeutic drugs and the levels of IL-6 and IL-1β were significantly lower in the soy peptide group than the placebo group [77]. An increase in blood IL-6 levels is associated with extra-articular symptoms of rheumatoid arthritis, such as general malaise, loss of appetite, weight loss, and a slight fever. The Disease Activity Score 28 [DAS 28, objective assessment of rheumatoid arthritis disease activity by physicians] and the Clinical Disease Activity Index [CDAI, patient's own subjective indicator of rheumatoid arthritis disease activity] were calculated from the degree of ADLs' improvement, the severity of pain, and subjective symptoms recorded by visual analogue scale [VAS]. The DAS 28 score of the peptide group was markedly decreased, and the CDAI of the peptide group was significantly lower than that in the placebo group.

These effects on cytokines were also evident in a cell experiment using articular chondrocytes from patients with rheumatoid arthritis [78]. In this in vitro cell study, treatment with soy peptide significantly suppressed the mRNA levels of MMP-3 and ADAMTS-4 enhanced by IL-1β stimulation. This finding also suggests that soy peptides may prevent the degradation of articular cartilage.

4. Physiological effects of other legume proteins

Soy protein has excellent health benefits, but many soybeans grown in the world are genetically modified organisms [GMOs]. There is no problem with the safety of GMO soybeans. However, from the perspective of security, the use of soy protein in foods tends to be withheld. Recently, the use of pea and lupin proteins instead of soy protein has increased worldwide. Initially, pea protein was a substitute for soybean protein as an ingredient with physical characteristics functions, after that, its beneficial health function has been reported mainly in sports nutrition. Mung bean protein has a structure very similar to that of β-conglycinin. Mung bean protein has been reported to be responsible for the beneficial physiological functions reported for β-conglycinin.

4.1 Pea protein

Field pea [*Pisum sativum* L.] is grown in 84 different countries and constitutes the largest percentage [36%] of total pulse production worldwide [79]. Global pea production has continuously increased over the last 30 years. In 2008, field pea was cultivated on over 10 million hectares worldwide with a total world production of

12.13 million tons [80]. The top 5 countries for pea production are Canada, Russia, China, India and the USA. The global market for pea protein is expected to reach 34.8 million US dollars by 2020 [81]. The physical and chemical properties of pea protein can significantly influence its behaviors in food processing, storage and consumption [82, 83].

Life expectancy continues to increase worldwide. In the United States, adults 65 years of age and older are projected to more than double from 600 million to 1.6 billion worldwide between 2015 and 2050 [84]. Proper body composition, physical fitness, and a healthy appetite have been reported to lead to successful aging with higher performance [85, 86]. Skeletal muscle mass and strength begin to decline at age 30, and the rate of these losses accelerates at age 60 [87]. Protein ingestion strongly increases muscle protein synthesis rates [88]. Amino acids serve as precursors for de novo muscle protein synthesis and can act as strong signaling molecules activating translation initiation via the mechanistic/mammalian target of rapamycin complex-1 (mTORC1) pathway [89]. It was shown that BCAA ingestion increases myofibrillar protein synthesis rates during recovery from exercise only in young males [90]. Whey protein isolate [WPI] was used as the animal protein source because of its high concentration of BCAAs and its ability to increase satiety in response to a mixed meal [91]. While whey protein supplementation is known to enhance adaptations to resistance training, not all athletes are able or willing to consume whey or animal proteins. Vegetarian athletes who want to stick to a plant-based diet or those with restrictions on other animal foods often rely on other plant proteins as an equivalent alternative to whey protein [92]. Self-identify as vegetarian in just over 5% of U.S. adults aged 18–34 years and self-awareness as vegan in more than half of these respondents are reported in a 2016 Harris Poll conducted by the Vegetarian Resource Group [93]. Meat Free Mondays' movement and an upsurge of plant-based protein food products in the marketplace strongly reflect the recent acceptance of these lifestyles [94].

Field pea contains a well-balanced amino acid profile [95]. Because of its availability, low cost, nutritional value and health benefits, pea protein has been widely used as a substitute for soybean or animal proteins in various functional applications [96–99]. Pea protein can also be used as a nutritional supplement for sports and exercises. Pea protein is an excellent source of BCAAs and has high and balanced contents of leucine, isoleucine and valine. Indeed, there are reports that pea protein is as useful as whey protein in sports nutrition (**Table 4**) [100–103].

In the future, pea protein is expected to be widely used as a sports nutritional supplement as well as a physical and functional ingredient in place of soybean protein.

4.2 Lupin protein

Lupin (*Lupinus* L.) is an ancient pulse "bean" crop, and in the new genus of modern agriculture, the lupin seeds have great potential for high-protein food, animal feed, food potential, soil fertility improvement, plants as cover crops, crop residues as stable feed, and soil improvement [104, 105]. Lupin is well known for its ability to fix nitrogen and grow on infertile soils, and is further known to be valuable in terms of cropping rotations during the growing season in agriculture with cereals, hay, oilseeds, beans of other legumes, and disease break crops for pasture [104, 106]. Wild indigenous lupins have bitter alkaloids. All modern species of *L. angustifolius* have total alkaloid levels in seeds of up to 200 mg/kg [0.02%] or less, which is 100 times lower than the seed alkaloid levels of nearly wild types. Compared to almost all food crops, lupins have only recently become of interest in modern crop breeding.

Study title	Design of study	Number of subjects	Duration of study	Outcome [significant difference]	Reference
Pea proteins oral supplementation promotes muscle thickness gains during resistance training: a double-blind, randomized, Placebo-controlled clinical trial vs. Whey protein.	Randomized, Double-Blind, Placebo-Controlled Study	161	12-wk	Biceps brachii muscle thickness↑	[100]
The Effects of Whey vs. Pea Protein on Physical Adaptations Following 8-Weeks of High-Intensity Functional Training (HIFT): A Pilot Study.	Randomized, Double-Blind, Placebo-Controlled Study	15	8-wk	Result of the resistance training program↑	[101]
Effects of Whey and Pea Protein Supplementation on Post-Eccentric Exercise Muscle Damage: A Randomized Trial.	Randomized, Double-Blind, Placebo-Controlled Study	109	5-day	Creatinine kinase↓, Myoglobin↓	[102]
The Short-Term Effect of Whey Compared with Pea Protein on Appetite, Food Intake, and Energy Expenditure in Young and Older Men.	Randomized, single-blinded crossover design	30	One shot [postprandial data]	Appetite↑, Energy expenditure↑, 24-h energy intake↑	[103]

Note: ↓ and ↑ signs represent decrease and increase, respectively, after supplement of active compounds [pea protein only or, pea and whey proteins].

Table 4.
Clinical studies of pea protein for sports nutrition.

There has been considerable interest in lupin seeds recently, and as a human health food, the seeds are very high in dietary fiber, gluten-free, and virtually starch-free, and therefore have a very low glycemic impact [107]. What makes lupins even more valuable is that there are no genetically modified (GM) bean varieties under commercial cultivation. World production of lupin seed increased quickly in the 1970s and is dominated by Australian production.

Lupin seeds are high in protein, with levels similar to soybeans. Their grains are also known to be high in total dietary fiber, ~40 g/100 g dry matter, making lupins unique among ancient grains and beans. The main category of protein in lupin grains is globulin, with albumin making up the remainder. The major globulin categories are α-conglutin [35–37 g/100 g total protein], β-conglutin [44–45 g/100 g total protein], γ-conglutin [4–5 g/100 g total protein], and δ-conglutin [10–12 g/100 g total protein] [108–111]. Nutritionally, the limiting amino acids in lupin protein are the sulfur-containing amino acids methionine and cysteine [112]. Compared to soy protein, which have a more complete essential amino acid profile, the lupin protein was reported to be slightly below the required level of sulfur-containing amino acids needed by adults [113]. However, Singla et al. reported that the sulfur-containing amino acid levels of lupin protein were similar to those of soy [114]. This discrepancy is probably due to differences in lupin protein varieties and production environments. Carvajal-Larenas et al. reviewed in detail the amino acid composition of whole lupin seeds and concluded that it varies slightly among species. In vitro digestibility is ~98% high for uncooked lupin protein and is similar to soybean [115].

In vitro models of Lupinus albus γ-conglutin have shown the biological activity that enhances insulin and metformin activity on intracellular glucose consumption, indicating the potential for regulation on blood glucose by γ-conglutin [116]. As a possible improvement of lipid metabolism, an increase in LDL receptor activity has been demonstrated by HepG2 cells [117]. Furthermore, isolated lupin proteins of have been reported to have hyperlipidemic, anti-atherogenic, and hypocholesterolemic effects in rabbits, rats, and chickens [118, 119]. Several clinical human studies have shown that lupin protein decreases total and LDL cholesterol, as well as triglyceride and reduce the glycaemic response (**Table 5**) [120–127].

In general, the anti-nutrient factor of lupins is considered to be low compared to other legumes such as soybeans. Specifically, protease inhibitors are present at very low levels and are of minor importance in lupin crops. Trypsin inhibitor activity is described as "negligible" in Lupinus species, "very strong" at 43–84 trypsin inhibitor units [TIU/mg] in soybeans, and high [17–51 TIU/mg] in common beans [128]. Bitter lupin seed varieties contain quinolizine alkaloids, which may be toxic to humans. These toxic effects were recently reviewed by Carvajal-Larenes et al. [115]. Therefore, its maximum legal level of 0.02 g/100 g lupine powder and food has been legislated in several countries. There were no differences in alkaloids in grains among commercial *L. angustifolius* cultivars from western Australia in the same region and season, and all samples were below the levels permitted for maximum human food use.

Lupin protein, a legume, is a plant protein with similar attributes to soybean protein [129] and can be a substitute for soybean in the food industry [130, 131]. Further extensive research is expected due to the need for alternatives to animal proteins.

4.3 Mung bean protein

The mung bean (*Vigna radiata* L.) is one of the most important edible legume crops, grown on more than 6 million ha worldwide (approximately 8.5% of the global pulse area) and consumed by most households in Asia [132]. For individuals who cannot afford animal proteins or those who are vegetarian, mung bean is comparatively low cost and is a good source of protein. Furthermore, mung bean protein is more easily digestible than protein in other legumes [133]. In addition to the nutritional properties of mung bean, it has been known that mung beans have various physical regulation functions from ancient times. In the Compendium of Materia Medica (the "*Bencao Gangmu*"), a well-known Chinese pharmacopeia, mung beans have recorded to be utilized as a traditional Chinese medicine for its detoxification activities, recuperation of mentality, ability to alleviate heat stroke, and regulation of gastrointestinal upset.

Mung bean protein isolate (MuPI) dose-dependently reduced plasma lipid levels, such as total cholesterol, triglycerides, and non-high-density lipoprotein cholesterol [non-HDL-C] in hamsters [134, 135]. The mechanism underlying the cholesterol-lowering activity of mung bean protein was speculated to increase fecal bile acid and sterol excretion and decrease cholesterol absorption and synthesis. This mechanism is the same as that reported for SPI [68, 69]. In another study,

Title	Design of study	Number of total subjects	Outcome [significant difference]	Reference
Lupin protein compared to casein lowers the LDL cholesterol: HDL cholesterol-ratio of hypercholesterolemic adults	Randomized, double-blind, placebo-controlled, parallel trial	43	Total-C↓, LDL-C↓, LDL: HDL-C ratio↓	[120]
Hypocholesterolaemic effects of lupin protein and pea protein/ fiber combinations in moderately hypercholesterolaemic individuals	Randomized, double-blind, parallel group design	175	Total-C↓	[121]
Lupin protein positively affects plasma LDL cholesterol and LDL:HDL cholesterol ratio in hypercholesterolemic adults after four weeks of supplementation: a randomized, controlled crossover study	Randomized, controlled, double-blind crossover study	33 hypercholesterolemic subjects	LDL-C↓, HDL-C↑, LDL:HDL-C ratio↓	[122]
Consuming a mixed diet enriched with lupin protein beneficiallyaffects plasma lipids in hypercholesterolemic subjects: A randomized controlled trial	Randomized, controlled, double-blind three-phase crossover study	72 hypercholesterolemic subjects	LDL-C↓, Homocysteine↓, TG↓, Uric acid↓	[123]
Australian sweet lupin flour addition reduces the glycaemic index of a white bread breakfast without affecting palatability in healthy human volunteer	Randomized, single-blind, cross-over design	11 healthy subjects	Postprandial blood glucose↓	[124]
Lupin and soya reduce glycaemia acutely in type 2 diabetes	Randomized, cross-over trial	24 diabetic adults	Postprandial blood glucose↓, Insulin response↑	[125]
Hypoglycemic effect of lupin seed γ-conglutin in experimental animals and healthy human subjects	Randomized, double-blind, parallel group design	15 adult healthy volunteers	Postprandial blood glucose↓	[126]
Short-Term Effects of Lupin vs. Whey Supplementation on Glucose and Insulin Responses to a Standardized Meal in a Randomized Cross-Over Trial	Randomized, controlled, cross-over trial	12 healthy male and female volunteers	Postprandial blood glucose↓, Insulin response↑	[127]

Note: ↓ and ↑ signs represent decrease and increase, respectively, after supplement of active compounds. Total-cholesterol (Total-C); low-density lipoprotein cholesterol (LDL-C); triglyceride (TG); high-density lipoprotein cholesterol (HDL-C).

Table 5.
Clinical studies of lupin protein on improving lipid and glucose metabolisms.

MuPI was found to lower blood triglyceride levels in normal rats by inducing adiponectin and reducing triglyceride synthesis via insulin signaling [136]. This mechanism is the same as that reported for β-conglycinin [23]. From these findings, MuPI can be expected to be more effective in improving lipid metabolism. The main component of MuPI, accounting for over 80% of the protein, is 8S globulin. 8S globulin exhibited the highest degree of sequence identity [68%] and structural similarity with β-conglycinin [137, 138]. MuPI is expected to exhibit a four times stronger beneficial function on human health than SPI, in which β-conglycinin accounts for only 20% of the total protein.

The positive effects of MuPI on glucose metabolism in pre-diabetes patients was confirmed. In recent double-blind, placebo-controlled clinical trial, the test group subjects were instructed to consume a total of 2.5 g of MuPI twice daily for 12 weeks, with pre-diabetes [fasting plasma glucose level of 110–125 mg/dL or 2-h plasma glucose level of 140–200 mg/dL by the 75-g glucose tolerance test]. In this study, MuPI was shown to suppress to increase fasting plasma glucose and insulin levels compared to the placebo group. Triglyceride levels significantly decreased in subjects with hyperlipidaemia [139]. Another double-blind, placebo-controlled clinical trial of 44 healthy subjects showed that after consumption of 3.0 g/d MuPI for 8 weeks, insulin levels and homeostatic model assessment of insulin resistance values significantly decreased, and plasma glucose levels showed a downtrend, although it was not significant [140]. The lack of a beneficial effect of MuPI on blood glucose concentrations may be attributed to the exclusion of volunteers with abnormal blood glucose concentrations in this study. In this study, the body compositions of subjects were measured by dual-energy X-ray absorptiometry. As a result, a decrease in body fat mass and an increase in lean body mass in the test group were revealed. Conversely, in the control group, body fat mass increased and lean body mass decreased. The differences in body fat mass and lean body mass within each group and between the test and control groups were not statistically significant. However, the adiponectin level in the test group significantly increased, and it decreased in the control group. There was a significant difference between the net changes in the test and control groups [140]. These findings indicate that MuPI might improve insulin sensitivity by decreasing the accumulation of visceral fat.

Non-alcoholic fatty liver disease [NAFLD] represents a spectrum of liver diseases involving hepatocyte dysfunction caused by hepatic triglyceride accumulation in these cells. The prevalence of NAFLD has increased with the increased prevalence of obesity and metabolic syndrome. NAFLD is now a common disease, affecting 30% of the US population and 20% of Asian and European populations [141]. Rodent studies have shown that SPI intake reduces hepatic triglyceride accumulation [142, 143]. The detailed mechanism underlying the hepatic triglyceride-reducing effect of SPI remains to be elucidated, but β-conglycinin is likely to play an important role [135]. Indeed, the administration of purified β-conglycinin results in an even stronger reduction in hepatic triglycerides than SPI administration [18, 144]. From these results, it is expected that MuPI also has a preventive effect on NAFLD by preventing hepatic triglyceride accumulation. The effect of MuPI on hepatic triglyceride accumulation elucidated the potential ability of MuPI to prevent NAFLD onset and progression in experiments using an atherogenic diet-induced NASH mouse model in mice fed a normal-fat or high-fat diet [145]. In the abovementioned clinical trial [140], Alanine aminotransferase [ALT] levels increased slightly in the control group, whereas significantly decreased in the test group. Of the blood test items, ALT is one of important indicators of the degree of liver dysfunction.

The released peptides obtained from mung bean protein hydrolysate may exhibit bioactivity as angiotensin I-converting enzyme (ACE) inhibitors, antioxidants, and anti-cancer Asiatic acid carriers due to their sequence characteristics [146, 147]. A peptide [<3 kDa], with a small molecular weight isolated from MuPI hydrolysates, was reported to show high ACE inhibitory and antioxidant activities, including DPPH radical scavenging activity, hydroxyl radical scavenging ability, and metal-chelating activity [146]. Three kinds of novel peptides exerting high ACE inhibitory activity were isolated from the alcalase hydrolysate of MuPI, and the amino acid sequences of these peptides were identified to be Lys-Asp-Tyr-Arg-Leu, Val-Thr-Pro-Ala-Leu-Arg, and Lys-Leu-Pro-Ala-Gly-Thr-Leu-Phe [148].

The relationships between MuPI intake, strength, and lean body mass (LBM) in underactive vegetarians were examined, and the impact of MuPI supplementation on these indices was recorded utilizing an eight-week, randomized, controlled feeding trial. LBM significantly correlated with grams of protein consumed daily and was also significantly correlated with grip strength and lower body strength [149]. Mung beans are inadequate in threonine, tryptophan, and the sulfur-containing amino acids cysteine and methionine, but they contain high levels of essential amino acids, notably leucine, lysine, and phenylalanine [150]. Although it is necessary to consider the amino acid balance, it is expected that MuPI will be widely used in the field of sports nutrition in the future.

5. Conclusion

If the current pace of population growth continues, the global population is expected to surpass 9 billion by 2050. In addition to this increase in population, the change of dietary habits of emerging countries due to their increased GDP will require, in 2050, we will need twice as much protein as we had in 2005.

So far, we have been able to meet the increasing demand for protein by improving the productivity of agriculture. However, in the future, this growth alone will not be enough to absorb the increase, and the balance between supply and demand will begin to collapse as early as 2030. This prediction is called the "protein crisis," and has recently begun to attract attention, especially in Europe and the United States. To solve this protein crisis, it is essential to use highly productive plant proteins as food ingredients instead of animal proteins, which are less efficient in production.

WHO has called for the need to address the double burden of malnutrition. This means that we need to look not only at nutrient deficiencies, but also at nutrient excesses. Obesity caused by over-nutrition and the resulting lifestyle-related diseases are spreading around the world. In this regard, consumer demand for plant protein-based products is high and expected to grow considerably in the next decade. A variety of soy and other plant-based functional foods have been recommended by many health organizations worldwide.

Currently, contributions to the SDGs (Sustainable Developing Goals) are being appealed around the world. There is widespread recognition that the replacement of animal protein with vegetable protein not only contributes to human health, but also to the earth health. Wider and prudent use of plant proteins in the diet can help to supply adequate high-quality protein for the population and may reduce the potential for adverse environmental consequences.

This chapter focused on the recently reported physiological functions of legumes-derived plant proteins, including soybeans. Further research is expected to lead to more widely use of the legumes introduced in this chapter and to the discovery and use of legumes with new functionalities.

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