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Mini Review

The Positive Impact of Soybean Proteins and Peptides on Chronic Health Issues- A Review

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Abstract

Lifestyle modifications have led to a widespread prevalence of chronic illnesses, posing significant challenges to public health and global economic stability. Key risk factors contributing to these conditions comprise abdominal obesity, insulin resistance, hypertension, dyslipidemia, heightened triglyceride levels, cancer, and related attributes. In recent years, there has been increasing interest in utilizing plant-based proteins for managing and preventing chronic diseases. Soybean, a cost-effective protein source containing approximately 40% protein, has garnered significant attention. Soybean peptides have been extensively investigated for their role in regulating chronic diseases. This review provides a concise overview of the structure, function, absorption, and metabolism of soybean peptides. Furthermore, it examines the regulatory effects of soybean peptides on key chronic diseases such as obesity, diabetes mellitus, Cardiovascular Diseases (CVD), and cancer. The review also discusses the limitations of existing functional research on soybean proteins and peptides in addressing chronic diseases, along with potential future research directions.

Keywords: Chronic diseases, Soybean peptides, Diabetes mellitus, Obesity, Cardiovascular diseases, Cancer

INTRODUCTION

As urbanization progresses and sedentary lifestyles become more prevalent, chronic diseases have emerged as a global public health concern (Aiello G et al., 2018). These conditions, which are non-communicable and multifactorial, develop slowly over time and persist for extended durations, encompassing a range of ailments rather than specific illnesses (Alberti KG et al., 2009). Chronic diseases can arise from various factors such as lifestyle choices, environmental influences, dietary habits, or genetic predispositions (Alghnam S et al., 2021). The global mortality attributed to chronic diseases saw an escalation from 28 million in 1990 to 36 million in 2008, further rising to 39 million by 2016 (Anderson E et al., 2019). It is estimated that over two-thirds of global fatalities are attributed to chronic diseases. According to the World Health Organization (WHO), in 2019, seven out of the top ten causes of death were attributed to non-communicable diseases (Astawan M et al., 2018). Currently, chronic diseases predominantly encompass obesity, diabetes, Cardiovascular Diseases (CVD), and cancer, serving as primary factors contributing to premature mortality among individuals (Belza A et al., 2013). The development of chronic diseases involves intricate pathogenic processes, such as disruptions in the protease network, which can result in dysregulation of the cellular signaling network (Brian Chia CS, 2021). The activity of matrix metalloproteinases (MMPs) and the dysregulation of the Phosphoinositide 3-Kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway could influence the progression of chronic conditions such as Cardiovascular Diseases (CVD), Type 2 Diabetes (T2D), and cancer (Cavaliere C et al., 2010). As metabolic disorders, chronic illnesses are linked to Metabolic Syndrome (MetS). MetS is not an ailment in itself but rather a holistic concept that encompasses factors contributing to heightened risks of specific diseases as shown in Figure 1 (Chalamaiah M et al., 2018). Studies have indicated that various elements of Metabolic Syndrome (MetS) substantially elevate the risk of chronic illnesses (Chang CL et al., 2013).

Furthermore, there is partial overlap between the risk factors for chronic diseases and the criteria used to define MetS (Chatterjee C et al., 2018). Consequently, Metabolic Syndrome (MetS) can serve as a predisposing factor for the onset of chronic diseases (Chen Z et al., 2019). Numerous ailments associated with both conditions have been recognized, encompassing obesity, Type 2 Diabetes (T2D), Cardiovascular Diseases (CVD), and cancer **(Figure 1)**.

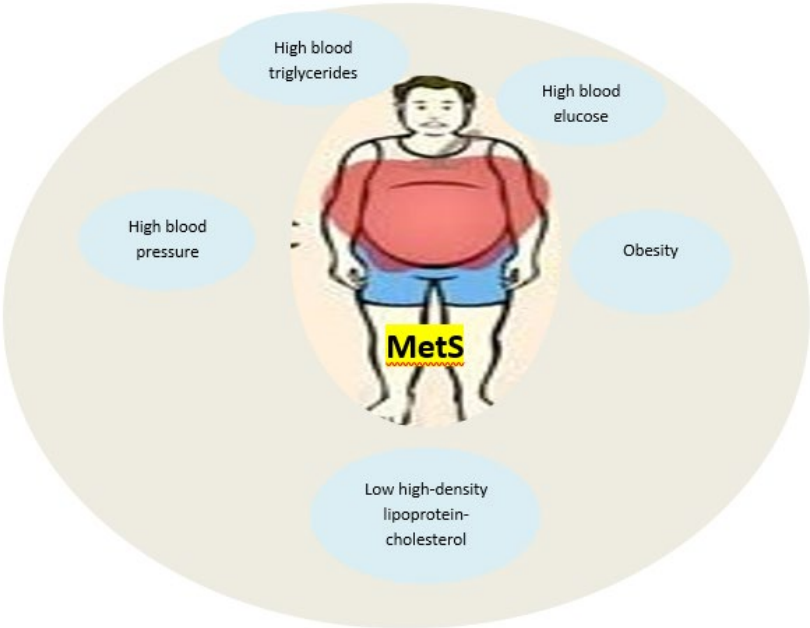

Figure 1. The primary diagnosis of Metabolic Syndrome (MetS) typically involves identifying three out of the five aforementioned conditions as part of the syndrome.

MATERIALS AND METHODS

Among the conditions listed (Figure 1), obesity stands out as a significant contributor to Metabolic Syndrome (MetS) (Christopoulou ME et al., 2023). Obesity can heighten the likelihood of insulin resistance, thereby contributing to the development of MetS (Cicero AF et al., 2017). In 2005, the International Diabetes Federation acknowledged obesity as an essential component in diagnosing MetS (Cole JB et al., 2020). Dr. Reaven contested this notion, suggesting that insulin resistance could be the primary driver behind Metabolic Syndrome (Dai W et al., 2017). Metabolic Syndrome (MetS) represents a significant risk factor for the development of Type 2 Diabetes (T2D) and Cardiovascular Diseases (CVD), as illustrated in Figure 2.

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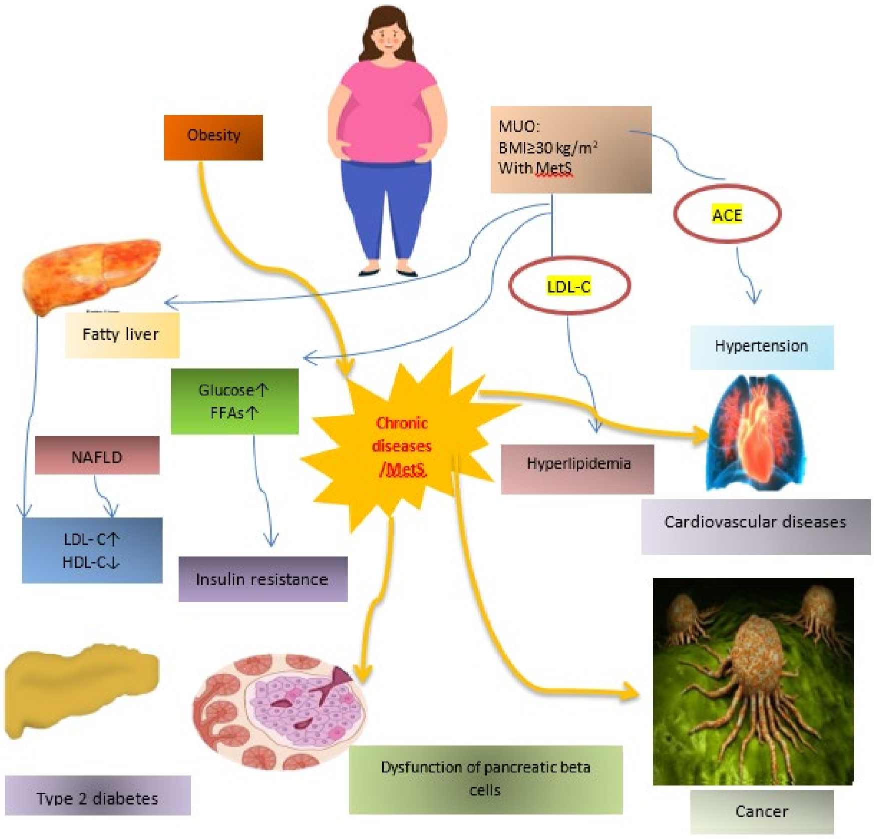

Figure 2. The connection between chronic diseases and conditions associated with Metabolic Syndrome (MetS) is depicted in the illustration, featuring elements from BioRender. Metabolic Unhealthy Obesity (MUO) and Nonalcoholic Fatty Liver Disease (NAFLD) are highlighted alongside factors such as low-density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C), Angiotensin-Converting Enzyme (ACE), and Free Fatty Acids (FFAs).

Obesity encompasses both Metabolic Healthy Obesity (MHO) and Metabolic Unhealthy Obesity (MUO) (Daliri EB et al., 2017). Although Metabolic Healthy Obesity (MHO) is transient and unstable, the majority of individuals with MHO will progress to the Metabolic Unhealthy Obesity (MUO) stage due to the accumulation of fat (Erak M et al., 2018). Morgan Mongraw Chaffin and her team discovered that Metabolic Healthy Obesity (MHO) transitions to Metabolic Unhealthy Obesity (MUO) when it surpasses a specific threshold (with an Odds Ratio (OR) of 1.60 and a 95% Confidence Interval (CI) of 1.14 to 2.25). Furthermore, individuals with MUO experienced a notable increase in Cardiovascular Disease (CVD) risk (Erdmann K et al., 2008).

Conversely, obesity can lead to the progression of Metabolic Syndrome (MetS) into diabetes, and Nonalcoholic Fatty Liver Disease (NAFLD), the prevalent metabolic liver disorder, represents a continuum linking these conditions (Fahed G et al., 2022). Around 30% of adults in the United States are affected by Nonalcoholic Fatty Liver Disease (NAFLD), with approximately 20% of cases occurring in individuals with obesity. In a meta-analysis comprising 24 studies and 35,599 individuals diagnosed with type 2 diabetes, the prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) among diabetic patients without obesity was 59.67%, whereas it rose to 77.87% among those with obesity. Metabolic Syndrome (MetS) results in elevated glucose levels in the body and the overproduction of free fatty acids. The dysfunction level of pancreatic beta cells was correlated with the severity of Metabolic Syndrom. Currently, treatments for chronic diseases typically involve interventions such as physical exercise, dietary adjustments, and medications targeting associated symptoms. The industry acknowledges bioactive peptides derived from food proteins as beneficial for health due to their cost-effectiveness and minimal side effects. Various bioactive peptides sourced from diverse foods have been identified for their health-promoting properties, including actions against hypertension, diabetes, and cancer. Research indicates that higher consumption of plant proteins is linked to a reduced likelihood of obesity, Cardiovascular Disease (CVD), diabetes, cancer, and other related conditions. Soybean peptides, a prevalent bioactive component extracted from soybean proteins, have been widely employed in various health applications, including combating obesity, diabetes, Cardiovascular Disease (CVD), cancer, and exhibiting antioxidant properties.

Soybeans, a traditional plant, have been cultivated in China for almost 5000 years. Soybeans were introduced to the United States in 1965. The cultivation of soybeans expanded in various countries, leading it to become a globally popular cash crop. Soybeans are rich in proteins, constituting approximately 40% of their total nutrients, making them a crucial plant-based source of dietary proteins. Soybean proteins encompass all twenty amino acids, including the nine essential amino acids. Soybean peptides are produced through the hydrolysis of soybean proteins using various proteases. They consist of oligopeptides containing 3–6 amino acids and have molecular weights ranging from 300 to 700 Daltons. The biological functions of soybean peptides are influenced by both their molecular weights and the specific sequences of amino acids they contain. While maintaining the same amino acid composition and proportions as soybean proteins, soybean peptides are characterized by enhanced absorption and stability. In previous studies, soy proteins and peptides have demonstrated safety and lack of toxicity, a crucial aspect for their continued utilization.

This paper provides an overview of the structure, function, absorption, and metabolic traits of soybean peptides. Additionally, it explores their potential impacts on managing and ameliorating chronic diseases.

Structural characteristics and metabolic pathways of soybean peptides.

Bioactive peptides are short sequences comprising 2–20 amino acids that have the ability to modulate or enhance physiological functions, thereby aiding in the prevention or treatment of chronic diseases. Soybean peptides are also produced through enzymatic hydrolysis, as depicted in Figure 3. The isolation and characterization of protein hydrolysates enable us to elucidate the connection between peptide structures and their functions. This is crucial for enhancing the bioavailability of bioactive compounds in the future **(Figure 3)**.

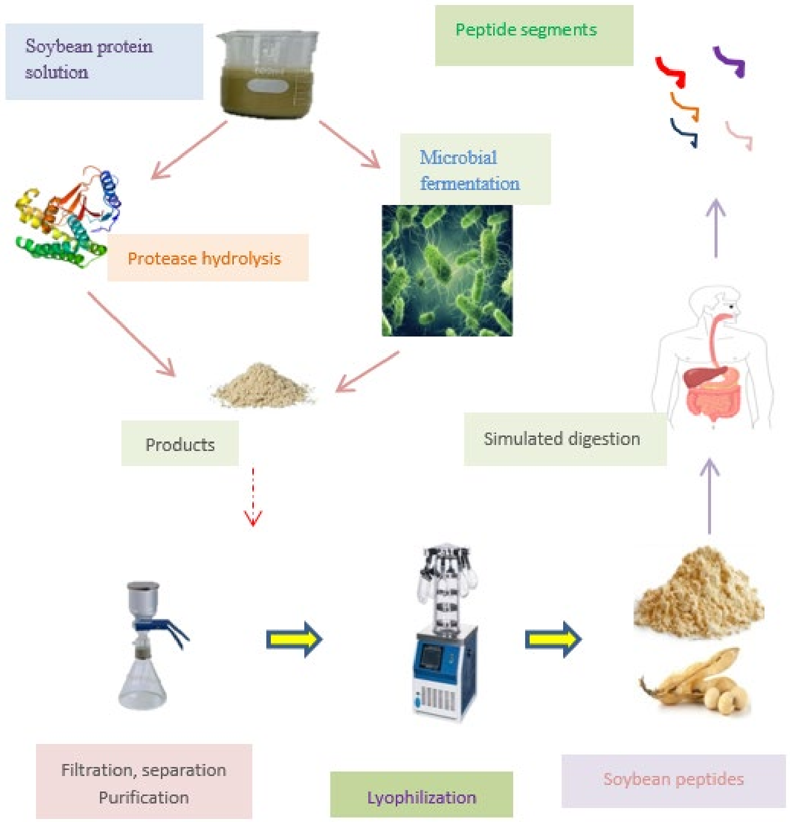

Figure 3. The method for preparing soybean peptide segments (with some visual elements sourced from BioRender) is described below.

Structure and function of soybean peptides

Comprehending the structures of bioactive peptides, which encompass factors like disulfide bond placement, amino acid composition and sequence, molecular weight, hydrophobicity, and other structural attributes, holds significant importance for devising new peptides and enhancing their effectiveness, bioavailability, as well as their physical and chemical properties. For example, peptide fragments containing three or more disulfide bonds exhibit greater stability. The capacity of peptides to bind to ACE and the antioxidant potential of soybean protein hydrolysates are contingent upon the existence of hydrophobic amino acids at the C-terminus. The inclusion of three aromatic amino acids (Trp, Tyr, and Phe), hydrophilic and basic amino acids (His, Lys, and Pro), as well as hydrophobic amino acids (Leu, Phe, and Val) in the polypeptide chains augments their antioxidant potential. Soybean β-conglycinin, a predominant protein in soybeans, constitutes 24.7–45.3% (w/w) of the total protein content. While it's commonly accepted that peptides with lower molecular weights exhibit potent antioxidant capabilities, the functional efficacy of peptides is also influenced by the processing techniques employed. For instance, a higher substrate concentration during the digestive process yields more small soybean peptides, consequently enhancing the free radical scavenging activity of α, α-diphenyl-β-picrylhydrazyl (DPPH), an important marker used to assess antioxidant efficacy. The interaction between hydrophobic amino acids and residues such as Cys, Glu, Tyr, Asp, Trp, and Gln in the sequence is also crucial for immune regulatory functions. Soybean peptides have been extensively investigated for their diverse functions, including lipid-lowering effects, antioxidant properties, anticancer activity, modulation of intestinal flora, immunomodulation anti-inflammatory effects, antihypertensive effects, antidiabetic properties, and various other physiological activities. However, there remains a scarcity of studies specifically examining the relationship between peptide structures and their functional outcomes. While certain peptides derived from soybean proteins have demonstrated diverse functions, there remains insufficient evidence to establish direct associations between specific functions and distinct structural characteristics. According to Daliri and colleagues, peptides possessing multiple biological activities are considered superior to those with singular functions. This perspective stems from the belief that peptides with multifaceted activities can provide broader and more comprehensive benefits. Therefore, further research is warranted to explore the generation of soybean peptides that are stable, possess specific structures, and exhibit multiple functional properties. This is because peptides with multiple activities can simultaneously fulfill several beneficial roles. Hence, further investigation is needed to explore efficient methods for deriving stable soybean peptides with specific structures and multifunctional properties.

Absorption and metabolism

Bioactive peptides have physiological functions beyond their nutritional significance. However, the majority of these peptides remain inactive within the parent protein, unable to carry out their functions. To activate their bioactivities, short peptides consisting of 2–20 amino acids need to be liberated from the parent proteins *via* enzymatic hydrolysis. Protein hydrolysates or short peptides exhibit greater biological activities compared to intact proteins or mixtures of amino acids. Following digestion in the gastrointestinal tract, certain bioactive peptides have the ability to be absorbed through the intestinal tract into the bloodstream, where they can reach their target organs and exert their effects. Meanwhile, others exert their effects locally within the gastrointestinal tract. The presence of intestinal epithelial cells poses a significant challenge to the absorption of food components. The action of proteases on the surface of these cells, which are characterized by microvilli, is likely pivotal in influencing the stability, integrity, and biological functions of peptides. Mature intestinal epithelial cells exhibit similar morphology and functionality to differentiated Caco-2 cells, expressing brush border peptidases and transporters. These cells serve as valuable in vitro models for investigating peptide stability, absorption, and transport. In assessing the efficient use of a bioactive peptide, researchers also employed differentiated Caco-2 cell lines as an intestinal model to study peptide absorption. Gilda Aiello and colleagues discovered that three soybean peptides (IAVPGEVA, IAVPTGVA, and LPYP) were absorbed to some extent by Caco-2 cells in vitro. These peptides were found to enhance cholesterol metabolism in HepG2 cells by inhibiting the activity of 3-hydroxy-3-methylglutamate CoA reductase (HMGCoAR). Apart from assessing absorption, Caco-2 cells are also utilized to examine the stability of bioactive peptides. This is due to their capability to express brush border peptidases and transporters, which can influence the stability and transport of peptide fragments. The transportation of the peptide KPVAAP was observed for duration of up to 60 minutes on both the apical and basolateral sides of the transwell, suggesting its stable absorption by Caco-2 cells. Similarly, the degradation of the soybean peptide segment, WGAPSL, was evaluated during its transportation through Caco-2 cells, indicating its ability to traverse the intestinal peptidase and mucus layer and be fully absorbed by the human body. This indicates that WGAPSL maintains favorable stability following digestion in the gastrointestinal tract. Upon entry into the body, bioactive peptides undergo enzymatic cleavage of peptide bonds by endopeptidases, resulting in the formation of oligopeptides. Subsequently, exopeptidases such as carboxypeptidase and aminopeptidase hydrolyze the N-terminal or C-terminal residues of these oligopeptides, converting them into individual amino. To enhance their stability and bioavailability, different biochemical approaches have been employed, including the use of unnatural amino acids and D-amino acids substitution, cyclization, chemical modification of N-terminal and C-terminal groups, main chain modification, and formulation into nanoparticles. Comprehending the metabolism and degradation of bioactive peptides by endogenous proteases holds significant importance in designing functional foods or drugs and enhancing the metabolic stability of peptides. Understanding the absorption and metabolism of soybean peptides is essential for determining their biological efficacy. Investigating there in vitro absorption rate and the potential pathways they might influence in vivo holds great significance.

The impact of soybean peptides on chronic diseases

Scientists are keen on investigating peptides and protein hydro lysates as potential therapeutic agents for preventing or managing chronic diseases. Soybean peptides, being potent bioactives sourced abundantly, have garnered significant interest, and their functions have been extensively studied (Table 1). This review focuses on examining the effects of soybean proteins and peptides on chronic diseases, encompassing areas such as combating obesity, diabetes, Cardiovascular Diseases (CVD), and cancer **(Table 1 and Figure 4)**.

Table 1. Outlines the roles of soybean proteins and peptides in the context of chronic diseases.

Function	Bioactive substance of soybean peptides	Detection model (females or males)	Main results
Anti-obesity effect	β-conglycinin	C57BL/6 mice (males)	Weight reduced
	β-conglycinin	C57BL/6 mice (males)	FGF21 increases
	β-conglycinin	Obese rats (males)	Abnormal fat and lipid levels reduced
	β-conglycinin	Rats (males)	Serum cholesterol dropped from 124 mg/dL, and liver triglycerides decreased from 214 mg to 163 mg.
	Soybean protein isolates	Obese rats (females)	AST levels reduced from 222.5 U/L to 103.4 U/L, and ALT levels decreased from 71.9 U/L to 56.2 U/L.
	Soybean proteins	Obese OLETF rats (males)	Serum cholesterol decreased to 142 mg/dL
Anti-CVD	VAWWMY/ Soy statin	Rats (males)	Serum and liver cholesterol levels were decreased to 0.03%.
	IAVPTGVA, IAVPGEVA	HepG2 cells.	HMGCoAR and LDL levels decreased
	Soybean protein hydrolysates	caco-2 cells	The solubility of micelles containing dietary cholesterol decreased
	Polypeptide content of soybean meal	Hypertensive rats (males)	ACE activity reduced
Anti-diabetes effect	Glu-Ala-Lys and Gly-Ser-Arg		The inhibitory effect of α-glucosidase activity was 45.89%.
	Soybean protein isolates and soybean peptides	Human (both)	The consumption of SPI led to a notable
	Soybean proteins	Patients with diabetes (both	After a period of two months, fasting blood glucose experienced a reduction of 1.68%
	VHVV	H9c2 cells and ICR mice	Cell apoptosis decreased (males) blood glucose decreased.
	Luna sin	NSCLC cell line H661	Reduced growth and multiplication of cancerous cells
	Luna sin	Human breast cancer cells	Decreased proliferation of cancer cells.
Anti-cancer effect	Germinated soybean	Human colon cancer cell lines peptides	After treatment with 10 mg/mL soybean peptide segments for 24 h, cell viability decreased by 82–66%.

Note: FGF21: Fibroblast Growth Factor 21 gene; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; SPI: Soybean Protein Isolates; HMGCOAR: 3-hydroxy-3-methylglutamate CoA reductase; LDL-C: Low-Density Lipoprotein Cholesterol; PCSK9: Protein Convert are Subtilisin/Kexin type 9; ACE: Angiotensin-Converting Enzyme; IC50: half maximal inhibitory concentration.

RESULTS AND DISCUSSION

The impact of soybean peptides on obesity

The significant rise in obesity rates has emerged as a critical global public health concern. As per the World Health Organization (WHO), an individual is classified as obese when their BMI reaches 30 kg/m², while a BMI of 25 kg/m² is indicative of being overweight. In 2016, over 39% of adults globally were classified as overweight, with approximately 13% falling into the obese category. Abdominal obesity is strongly linked to chronic metabolic conditions like Type 2 Diabetes (T2D) and Cardiovascular Disease (CVD). Numerous approaches exist for addressing obesity, including medications, surgical procedures, and dietary modifications, with diet being the most straightforward and cost-effective method for weight reduction without adverse effects. Protein is commonly employed as a dietary strategy for weight loss due to its notable satiety-inducing effect. In a randomized crossover study, it was found that fermented soybean exhibited superior regulatory effects on appetite-controlling hormones (Acyl-ghrelin, insulin, and arginine) in obese females compared to non-fermented soybean. The study indicated an increased insulin-stimulating effect, possibly due to the fermentation process accelerating protein degradation rates and enhancing the bioavailability of short peptides. Recent research suggests that components of soybean protein may contribute to an anti-obesity effect. Constituting approximately 20% of soybean proteins, β-conglycinin plays a crucial role in the beneficial impacts associated with soybean proteins. Research has demonstrated that β-conglycinin has the potential to lower serum triglyceride and cholesterol levels, suggesting its potential anti-obesity properties. A diet incorporating soybean protein led to weight and fat tissue reduction in C57BL/6 mice, indicating the anti-obesity function of β-conglycinin. Following a singular administration of β-conglycinin, there was a notable increase in both Fibroblast Growth Factor 21 gene (FGF21) expression within the liver and circulating FGF21 levels in the mice.

As demonstrated earlier, β-conglycinin, being the primary constituent of soybean proteins, holds promise as a potential agent for combating obesity. Further research is necessary to explore the anti-obesity properties of β-conglycinin and elucidate its underlying mechanisms. It could emerge as a viable option for individuals with obesity seeking to manage their weight.

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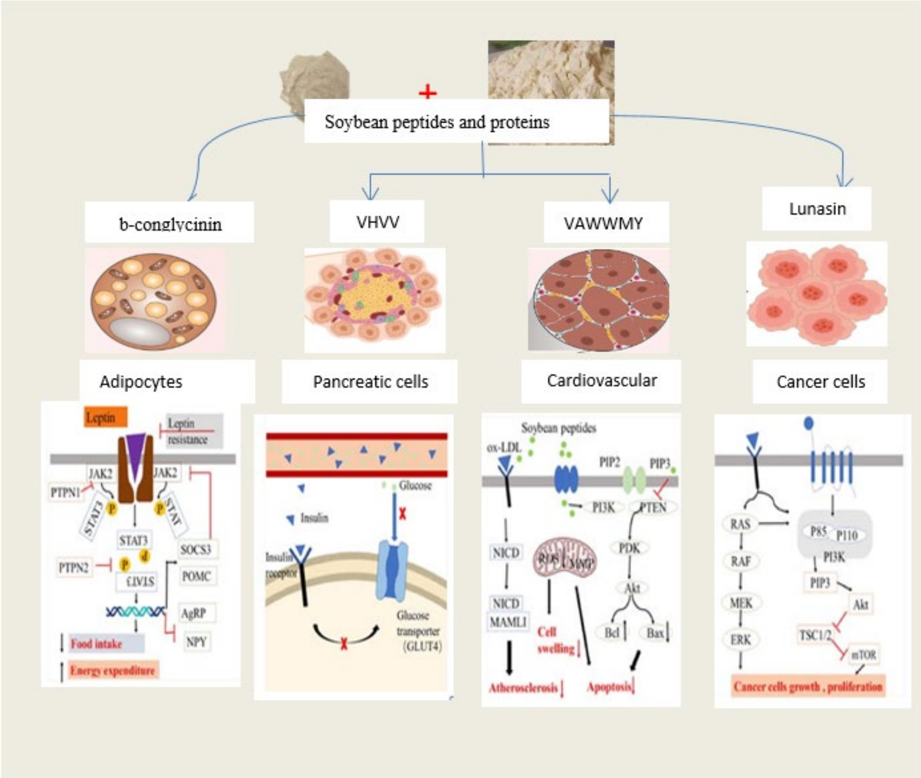

Figure 4. Illustrates partial potential mechanisms underlying the diverse activities of soybean proteins and peptides on chronic diseases, with certain graphical elements sourced from BioRender. Key components and pathways involved include JAK (Janus Kinase), STAT (Signal Transducer and Activator of Transcription), PTP (Protein Tyrosine Phosphatases), SOCS (Suppressor of Cytokine Signaling), POMC (Proopiomelanocortin), AgRP (Agouti-Related Peptide), NPY (Neuropeptide Y), PIP2 (Phosphatidylinositol-4,5-biphosphate), PIP3 (Phosphatidylinositol-3,4,5-triphosphate), ox-LDL (oxidized Low-Density Lipoprotein), PI3K (Phosphoinositide 3-Kinase), PTEN (Phosphatase and Tensin homolog), ROS (Reactive Oxygen Species), MMP (Matrix Metalloproteinase), NICD (Notch Intracellular Domain), MAML1 (Mastermind-like proteins), MEK (Mitogen-activated protein kinase), ERK (Extracellular signal-Regulated Kinases), and mTOR (mammalian Target of Rapamycin).

Soybean proteins also participate in regulating the gastrointestinal microbiome and maintaining bile acid balance. The varied microbiota significantly contributes to obesity development, and their interactions, facilitated by signaling molecules or communication, can be sustained through dietary interventions or supplements. Preserving the microbiota via dietary approaches could hold significant value in chronic disease management. Intake of soybean proteins enhanced gut microbiota, boosted intestinal microbial diversity, and facilitated improved transmission of bile acid metabolism signals. Feeding with Soybean Protein Isolate (SPI) over an 8-week period led to a reduction in fat denaturation in the liver and lowered levels of Aspartate Aminotransferase (AST) and Alanine aminotransferase (ALT) in the bloodstream. These outcomes were advantageous for maintaining bile acid balance, and the impact was more pronounced compared to casein.

The impact of soybean peptides on diabetes mellitus

Currently, diabetes has emerged as a significant global public health concern, ranking as the seventh leading cause of death worldwide. It imposes a substantial burden on both the families of affected individuals and the global economy. As per reports from the WHO and the International Diabetes Federation, the incidence of diabetes continues to rise annually. Diabetes is characterized as a systemic metabolic disorder resulting from irregular blood glucose levels, and it stands as one of the fastest-growing and prevalent chronic illnesses globally. There exist two primary types of diabetes: Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D). T1D predominantly manifests as an autoimmune condition triggered by genetic factors, often emerging in childhood due to diminished pancreatic beta cell function. Soybean proteins are recognized as hypoglycemic functional food items due to their composition of specific amino acids such as Leucine (Leu), Arginine (Arg), Alanine (Ala), Phenylalanine (Phe), Isoleucine (Ile), Lysine (Lys), and Methionine (Met). These amino acids have the capacity to stimulate insulin secretion and function as trypsin inhibitors. Jun Tang and colleagues conducted an analysis on the association between the consumption of legumes, including soybean products, and the incidence of Type 2 Diabetes (T2D). Their findings revealed a negative correlation between certain soybean components, such as soybean isoflavones and soybean proteins, and the risk of developing T2D. Specifically, an increment of 10 grams of soybean protein per day was associated with a 9% reduction in the risk of T2D. The consumption of soybean proteins exhibited a negative correlation with diabetes risk in women in a dose-dependent fashion, although no such correlation was observed in men.

A review examining the structure, function, and mechanism of plant compounds with therapeutic and mitigative potential in Type 2 Diabetes (T2D) indicated that soybean proteins and bioactive compounds contribute to the regulation of blood glucose levels. These investigations revealed that the structural configuration of soybean proteins, along with their unique amino acids, can enhance the sensitivity of pancreatic β cells and promote insulin secretion. Consequently, certain soybean proteins and their derived bioactive compounds have the potential to serve as effective agents for blood glucose regulation.

Dipeptide Peptidase-IV (DPP-IV), α-glycosidase, and α-amylase are pivotal enzymes directly involved in blood glucose regulation, and inhibiting these enzymes represents an effective approach for managing Type 2 Diabetes (T2D). Gonzalez-Montoya and colleagues obtained soybean peptides of varying molecular weights through simulated gastrointestinal digestion *in vitro*. Their research revealed that peptides within the range of 5–10 kDa exhibited inhibitory effects on DPP-IV, α-amylase, and α-glycosidase. Further separation of these peptides led to the identification of four components, with three containing predominantly polypeptides featuring encrypted dipeptide and dipeptide amino acid sequences. It is suggested that the structure of these peptides may be the primary factor contributing to their effectiveness in inhibiting diabetes-related enzymes. VHVV, a short peptide extracted from soybean protein hydrolysates, has demonstrated the ability to enhance the viability of H9c2 cells under high glucose conditions. Furthermore, VHVV at a concentration of 10 µg/mL decreased the occurrence of apoptosis in H9c2 cells and lowered postprandial blood glucose levels in diabetic mice. Additionally, VHVV supplementation improved the structural integrity and quantity of pancreatic cells.

While soybean proteins and peptides boast favorable amino acid sequences and absorption properties, the bulk of research predominantly revolves around investigating the phenotype of diabetic mice, with the underlying mechanisms remaining elusive. Further comprehensive research is warranted to delve deeper into this area. Additionally, refining the screening, separation, and purification processes of peptides exhibiting anti-diabetic effects will provide valuable insights into the regulation and treatment of diabetes.

The impact of soybean peptides on Cardiovascular Disease (CVD)

Cardiovascular Disease (CVD) encompasses a range of conditions affecting the heart and blood vessels, such as high levels of lipids and cholesterol, elevated blood pressure, the development of plaque in arteries (atherosclerosis), and other significant ailments. The likelihood of developing CVD is strongly associated with insulin resistance and obesity. Currently, cardiovascular disease contributes to 46.2% of non-communicable disease fatalities worldwide, making it a primary factor in premature mortality. The potential benefits of soybean proteins in enhancing and preventing Cardiovascular Disease (CVD) have garnered significant interest. As far back as 1999, the United States Food and Drug Administration (FDA) sanctioned the inclusion of soybean protein content on food labels for CVD prevention. The FDA endorsed the health claim that consuming 25 grams of soybean proteins daily can lower the risk of CVD. A comprehensive meta-analysis revealed a clear inverse relationship between consuming soybeans and the risk of Cardiovascular Disease (CVD). The reason behind this could be the potential of bioactive peptides present in soybeans to decrease the overall cholesterol levels in the body. Another meta-analysis indicated that consuming 25 grams of soybean proteins per day can lead to a 3-4% decrease in Low-Density Lipoprotein Cholesterol (LDL-C) levels among adults. Both elevated levels of lipids in the blood (hyperlipidemia) and high levels of cholesterol (hypercholesterolemia) significantly increase the risk of Cardiovascular Disease (CVD). In 2010, researchers discovered a novel peptide called "soystatin" in soybeans, specifically in soybean glycine, which has been shown to reduce cholesterol levels. Soystatin, represented by the sequence VAWWMY, has a similar ability to bind with bile acids as pharmaceutical drugs used for lowering cholesterol. Interestingly, soystatin is the sole low-cholesterol peptide identified in soybeans. Three peptides derived from soybean globulin glycine (IAVPTGVA, IAVPGEVA, and LPYP) were found to inhibit the activity of HMGCoAR, activate the LDLR-SREBP2 pathway, and enhance LDL absorption in vitro. Consequently, these peptides regulated cholesterol metabolism in HepG2 cells. In a separate investigation, hydrolysates of digested soybean protein were observed to decrease the solubility of dietary cholesterol micelles by 37.6% and reduce absorbability by 18.99% in Caco-2 cells. Anomalies in blood lipid levels, particularly the increase in plasma LDL-C levels, pose a significant risk for Cardiovascular Disease (CVD). In addition to pharmaceutical approaches, researchers are increasingly focusing on nutritional interventions to prevent chronic illnesses. In a previous study, two soybean peptides, YVVNPDNDEN and YVVNPDNNEN, were found to lower LDL-C levels by inhibiting HMG-CoAR activity. Furthermore, the latter peptide also decreased the protein expression of Protein Convertase Subtilisin/Kexin type 9 (PCSK9), a crucial regulator of LDL-R. In a separate investigation, the oral intake of two additional soybean peptides, ALEPDHRVESEGGL and SLVNNDDDRDSYRLQSGDAL, increased Trans-Intestinal Cholesterol Excretion (TICE), suppressed the expression of cytochrome P450 family enzymes (CYP7A1 and CYP8B1), decreased bile acid production, and enhanced cholesterol elimination from the liver. As a result, both peptides demonstrated efficacy in lowering blood lipid levels. High blood pressure, known as hypertension, is a significant contributor to Cardiovascular Disease (CVD). Successful management of hypertension can alleviate the prevalence of CVD among individuals affected by elevated blood pressure. The soybean peptide VHVV demonstrated inhibition of ACE activity in rats with hypertension and triggered activation of the SIRT1-PGC1α/Nrf2 pathway. This resulted in decreased synthesis of inflammatory factors in the kidneys and reduced apoptosis of renal cells, indicating VHVV's potential to ameliorate renal damage caused by hypertension. In spontaneously hypertensive rats, administration of soybean oligopeptide at a dosage of 4.50 g/kg for a period of 30 days led to notable decreases in both systolic and diastolic blood pressure, along with alterations in the quantity and concentration of angiotensin II. Research into the blood pressure-reducing properties of soybean peptides has predominantly concentrated on their ACE inhibitory activity, with only a limited number of studies exploring the direct impact of soybean peptides on blood pressure. Further investigations are necessary to examine the direct blood pressure-lowering effects in living organisms and to assess the anti-hypertensive effects on Cardiovascular Disease (CVD). There have been limited studies examining the impact of soybean peptides on Cardiovascular Disease (CVD), with only a small number of peptides identified. Additional research is required to identify more potent peptides that regulate CVD and to explore the underlying mechanisms responsible for the peptides' anti-CVD activity.

The influence of soybean peptides on cancer

Cancer now ranks as the second most common cause of death in the United States. Over 600,000 individuals in the United States succumbed to cancer in the year 2021. Conventional cancer treatments like medication therapy and chemotherapy come with high costs and can lead to adverse reactions or complications. Recently, there have been reports on various anti-tumor peptides, among which are soybean peptides. These soybean peptides, being a relatively cost-effective approach, are anticipated to have significant importance in both preventing and alleviating cancer progression.

Lunasin is a bioactive peptide consisting of 43 amino acids and with a molecular weight of 5.5 kDa. It was first discovered in soybeans. Research indicates that Lunasin possesses both chemopreventive and therapeutic properties. Studies have demonstrated that Lunasin can efficiently suppress the growth of the Non-Small Cell Lung Cancer (NSCLC) cell line H661 by hindering the G1/S phase transition of the cell cycle and modifying the expression of associated protein kinase complex components. Lunasin exhibited a notable inhibitory impact on the proliferation of human breast cancer cells. The inhibitory rates of Lunasin derived from transgenic soybeans and conventional wild-type soybeans were 43% and 23.8%, respectively. At concentrations of 40 and 80 μM, Lunasin notably enhanced apoptosis in colorectal cancer HCT-116 cells. This effect was achieved by decreasing the levels of the DNA repair enzyme (PARP) protein, a marker of cell apoptosis, and elevating the expression of caspase-3 protein. Additionally, Lunasin contributed to inhibiting tumorigenesis by prolonging the G1 phase. Gonzalez-Montoya and co-workers conducted experiments involving the treatment of three human colon cancer cell lines (Caco-2, HT-29, and HWT-116) with peptides of various lengths obtained through simulated in vitro gastrointestinal digestion. Their findings indicated variations in the inhibitory effects of germinated soybean peptides of different lengths on cancer cell proliferation. Further investigation into the mechanisms underlying the activity of the most potent peptides and their potential protective impact on colon health in animal models with colon cancer is required. Soybean peptides of varying molecular weights demonstrated varying degrees of inhibition on cancer cell proliferation in human blood, breast, and prostate. Notably, the 10–50 kDa peptide derived from the N98-4445A soybean strain exhibited a 68% inhibition of CCRF-CEM blood cancer cells.

Cancer, being a chronic illness, currently lacks a definitive cure. Research on the anti-cancer properties of soybean peptides has shown promise in inhibiting cancer cells. However, only a limited number of studies have delved into the anti-cancer potential of soybean peptides. Further research will be necessary to systematically screen and explore the anti-cancer effects of additional soybean bioactive compounds in animal models with various types of cancers.

CONCLUSIONS

Chronic diseases are complex conditions with multifaceted pathogenic mechanisms. Due to lifestyle changes, they have emerged as the primary cause of human mortality globally. Consequently, there is a collective endeavor among researchers to identify bioactive substances capable of regulating and treating chronic diseases. Bioactive peptides, increasingly recognized for their health-enhancing properties, hold significant promise in preventing and treating chronic illnesses. Beyond providing nutrition, food protein peptides have the potential to exert additional functions by modulating specific biochemical pathways. Soybean-derived peptides have garnered considerable attention for their potent anti-obesity, anti-diabetic, Cardiovascular Disease (CVD) regulation, and anti-cancer activities, all of which are pivotal in chronic disease prevention and management. Following digestion, most peptides can be efficiently absorbed by intestinal cells and transported to their respective target organs and cells.

The paper examined the bioactive properties of soybean proteins and peptides, discussing their structural aspects. It provided a brief overview of their absorption and metabolism within the body, and extensively discussed their roles in addressing chronic diseases such as obesity, diabetes, Cardiovascular Diseases (CVD), and cancer. Previous studies suggest that soybean proteins and peptides possess significant potential in combating chronic diseases. Further exploration is warranted to uncover additional bioactivities and the underlying mechanisms responsible for these functions.

Prospect

Over the past two decades, soybean proteins and peptides have garnered significant interest due to their diverse array of functions. Despite exhibiting fewer side effects compared to drug therapy, their efficacy is not as pronounced. Research into the functional aspects of soybean peptides is extensive yet lacks precision.

While single-functional soybean peptides have been extensively researched, the exploration of multifunctional peptides remains a challenging endeavor. There is a pressing need to transition from studying single-functional peptides to investigating multifunctional peptides in future research. This shift should concentrate on refining the method of protein hydrolysis, considering that protein hydrolysates comprise complex mixtures of peptides, with only certain peptides exhibiting bioactive functions.

Despite the multiple biological activities demonstrated by soybean peptides, their susceptibility to gastrointestinal proteases and peptidases may result in a loss of activity before reaching target organs. This consideration underscores the necessity for in vivo or clinical validation before considering them as a viable treatment option. The application of advanced multi-omics technology and bioinformatics holds significant potential in this regard. Soybean peptides hold significant promise for enhancing human health, yet there remains a dearth of clinical data supporting their efficacy. Concerning their commercial viability, further research is necessary to enhance production technology and optimize their bioavailability while maintaining quality standards.

Ultimately, prolonged or excessive intake of soybean peptides may lead to allergic reactions, side effects, or diminished digestive capacity in a minority of individuals. It is essential for further research to delve into determining the optimal dosage and duration of soybean peptide consumption to ensure effectiveness while minimizing potential adverse effects in this subset of the population. Addressing these considerations comprehensively will enable soybean peptides to make a substantial contribution to the prevention and treatment of chronic diseases.

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