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Linking the chemistry and physics of food with health and nutrition

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2 **Plant proteins for human health: current status and future needs**

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11 Abstract

12 Plant based protein consumption is increasingly recognized for its therapeutic potential in
13 managing metabolic health and preventing chronic diseases. This review provides a
14 comprehensive analysis of the physiological impacts of plant proteins, including their roles in
15 satiety regulation and weight management via the modulation of appetite regulating hormones. We
16 examine how plant proteins optimize lipid metabolism and reinforce gut homeostasis by promoting
17 a diverse microbiota and increasing the production of short chain fatty acids. Furthermore, we
18 dissect the mechanisms through which plant proteins and their digestion derived peptides attenuate
19 the pathogenesis of cardiovascular disease, type 2 diabetes, and chronic kidney disease. Specific
20 attention is given to the modulation of intracellular signaling pathways such as PI3K-Akt and the
21 regulation of the renin angiotensin system. The review also highlights that the health efficacy of
22 plant proteins is highly dependent on the food matrix, where synergistic interactions between
23 proteins, fiber, and phytochemicals are critical. Finally, the influence of food processing on peptide
24 bioaccessibility and advocate for a process matrix function paradigm in future research is discussed.
25 In conclusion, these insights underscore the role of plant proteins as functional components that
26 are essential for developing sustainable and precise nutritional strategies to mitigate the global
27 burden of non-communicable diseases.

28 **Keywords:** plant proteins, pulse, composition, non-communicable diseases, bioactive peptides,
29 metabolic health



30 1. Introduction

31 Proteins are indispensable macronutrients that provide essential amino acids and serve as
32 structural and functional components of human tissues, supporting growth, repair, and metabolic
33 homeostasis. The 2025-2030 Dietary Guidelines for Americans significantly increase
34 recommended protein intake from the previous 0.8 g/kg standard to 1.2 to 1.6 grams of protein per
35 kg of body weight.¹ In general, humans can obtain dietary proteins from a wide range of sources,
36 including animal, dairy, plant, microbial, marine, and insect origins. With increasing
37 environmental and sustainability concerns, a marked shift in consumers preferences toward
38 proteins derived from plant has been observed. Traditionally, plant proteins are central to food
39 structure and functionality, governing the formation, stability, and sensory properties of many food
40 systems. For instance, wheat gluten confers viscoelasticity to dough systems, whereas soy proteins
41 exhibit strong gelation and water-holding capacity, properties that are widely exploited in
42 structured plant-based foods.² More recently, the structural potential of plant proteins has been
43 extended to advanced colloidal system development, such as hydrogels, oleogels, and hybrid bi-
44 gels, which enable precise modulation of texture, fat structuring, and digestion behavior.³ These
45 plant protein-based networks hold significant promise for developing healthier fat-reduced foods
46 and designing next-generation plant-based products with tailored functional properties.

47 Plant proteins are derived from a wide range of botanical sources, which are commonly
48 classified into four major categories: legumes, cereals, oilseeds, and emerging novel sources.
49 Legume proteins, such as those from soy, pea, and lentil, are among the most extensively studied
50 due to their relatively high protein content and distinctive amino acid composition. Cereal proteins,
51 including wheat, rice, and maize, constitute a major proportion of global dietary protein intake and
52 are closely associated with staple food matrices that determine both technological functionality



53 and nutritional outcomes⁴. Oilseed proteins, obtained primarily from defatted meals of crops such
54 as peanut, rapeseed, and sunflower, represent an underutilized yet protein-rich resource with
55 diverse structural characteristics.⁵ Beyond these traditional sources, increasing attention has been
56 directed toward novel plant proteins from leafy biomass, reflecting the growing interest in
57 expanding the diversity and sustainability of plant-based protein supplies. These protein sources
58 exhibit substantial heterogeneity in composition, structure, and functionality, underscoring the
59 need to consider protein origin when evaluating their nutritional and health-related roles.⁶

60 Plant proteins, particularly those derived from legumes such as soy and peas, provide broad
61 health-promoting benefits primarily mediated by their unique amino acid composition and
62 synergistic food matrix effects.⁷ At the protein level, plant proteins provide diverse amino acid
63 profiles and encrypted bioactive sequences that have been associated with improved metabolic
64 regulation, cardiometabolic risk factors, and inflammatory status. Substitution of animal protein
65 with plant protein sources has consistently been linked to favorable outcomes in body weight
66 control, blood lipid profiles, and glycemic regulation, supporting their relevance in the prevention
67 and management of chronic diseases such as cardiovascular disease, diabetes mellitus, and chronic
68 kidney disease.⁸ In addition to the protein fraction itself, increasing attention has been directed
69 toward the synergistic role of the plant food matrix, in which proteins coexist with dietary fiber,
70 phytochemicals, and other bioactive constituents. For instance, in soy-based foods, dietary fiber
71 and associated phytochemicals such as isoflavones work together to regulate satiety signals,
72 manage energy balance, and modulate gut microbiota composition through prebiotic activities.
73 Together, current evidence suggests that the health impacts of plant proteins are multifactorial and
74 context-dependent, highlighting the importance of considering both protein source and food matrix
75 when evaluating their role in human nutrition.



76 This review aims to consolidate current knowledge on the relationships between plant
77 proteins and human health. In particular, the roles of plant proteins on satiety, weight management,
78 and muscle protein synthesis, as well as their effects on lipid metabolism and gut health are
79 systematically discussed. Evidence regarding the potential plant proteins in preventing and
80 management of non-communicable diseases, particularly cardiovascular disease, diabetes mellitus,
81 and chronic kidney disease, is critically evaluated. Finally, this review highlights key research
82 priorities, including the comparative efficacy of different plant protein sources, the role of co-
83 existing constituents within plant food matrices, and the bioactivity of protein-derived peptides
84 released during digestion.

85 **2. Satiety and weight management**

86 Foods rich in fat, dietary fiber, and protein are generally associated with prolonged satiety
87 compared with those high in rapidly digestible carbohydrates. Among these macronutrients,
88 dietary protein plays a particularly prominent role in appetite regulation, with consistent effects
89 observed across acute feeding studies as well as short- to medium-term dietary interventions. As
90 illustrated in **Figure 1**, protein-induced satiety including plant proteins has been widely attributed
91 to coordinated changes in gastrointestinal and endocrine signaling, including increased secretion
92 of anorexigenic hormones such as glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), and
93 peptide YY (PYY), alongside suppression of the orexigenic hormone ghrelin.⁹ These hormonal
94 responses are thought to contribute to reduced hunger perception and enhanced postprandial
95 fullness, although their translation into subsequent energy intake remains variable.



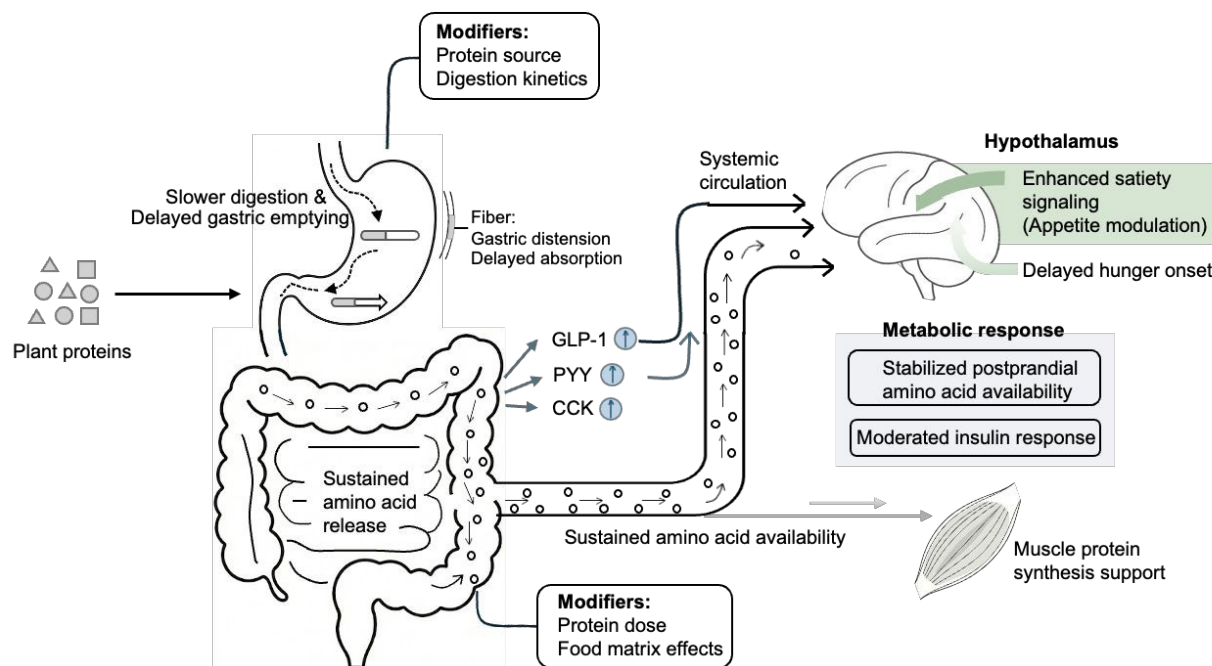


Figure 1. Mechanistic pathways of plant protein-induced satiety and weight management

Energy expenditure has also been proposed as a contributor to protein-induced satiety, particularly under sustained high-protein dietary conditions, and to a lesser extent following single high-protein meals. While it was previously thought that this mechanism might be less pronounced for plant-based sources, recent evidence suggests plant proteins can effectively modulate energy intake without necessarily altering systemic thermogenesis. For instance, a 50 g dose of soy protein was found to significantly enhance subjective satiety and reduce subsequent energy intake, despite no significant differences in diet-induced thermogenesis compared to carbohydrate controls.¹⁰ Crucially, the role of plant proteins in supporting muscle protein synthesis is a vital but often overlooked component of weight management. By providing the essential amino acid substrates to maintain metabolically active lean mass, plant proteins help prevent the decline in basal metabolic rate typically observed during weight loss, thereby supporting long-term energy homeostasis.



111 The satiety-inducing capacity of plant proteins is further influenced by postprandial
112 metabolites and specific amino acid profiles. High-protein soy-based meals (25% of energy) have
113 been shown to elicit greater satiety ratings compared to normal-protein counterparts, an effect
114 associated with elevated concentrations of metabolites like taurine and increased insulin
115 responses.¹¹ However, the satiety capacity is not uniform across all botanical sources. Specific
116 intervention studies highlighted that pea protein (e.g., NUTRALYS®) often elicits stronger acute
117 appetite suppression and more pronounced hormonal responses (e.g., CCK and PYY) compared
118 to soy protein. This superiority in acute satiety is likely driven by its distinct amino acid profile
119 and its tendency to form transient aggregates during gastric digestion, which delays nutrient
120 emptying more effectively than the relatively faster-digesting soy protein.¹² Furthermore,
121 fortifying foods with specific amino acids, such as L-arginine in legume-based cookies, has been
122 demonstrated to strengthen insulinemic responses and satiety hormone release, highlighting the
123 potential for targeted amino acid modulation to enhance the functional properties of plant-based
124 foods.¹³

125 Protein digestibility is another key determinant of physiological function. Many plant proteins
126 exhibit slower digestion kinetics due to their inherent globular structures and the presence of
127 antinutritional factors. This leads to a more sustained release of amino acids, as exemplified by
128 pea protein that forms transient aggregates during gastric digestion. This results in prolonged
129 aminoacidemia, extending the activation of central nervous system pathways involved in appetite
130 control.¹⁴ From an anabolic perspective, while the "slow" nature of some plant proteins might
131 result in a lower peak in muscle protein synthesis compared to rapidly digested whey, the sustained
132 amino acid supply may be advantageous for maintaining net protein balance over a longer
133 postprandial period. Moreover, food processing, such as extrusion, can decouple the relationship



134 between digestibility and satiety. Texturized vegetable protein (TVP) has been shown to induce
135 lower energy intake than meat, despite lower in vitro digestibility, suggesting that the physical
136 structure created during processing may prolong gastric retention.¹⁵

137 A critical factor that has long been underestimated is the impact of food matrix which may
138 ultimately be more crucial than the origin of protein alone. Dietary fiber, a major constituents of
139 plant protein, contributes to satiety through gastric distention, prolonged CCK secretion, and the
140 production of short-chain fatty acids (SCFAs) via colonic fermentation. Legume-based meals
141 (beans/peas) have been shown to induce 12-13% lower subsequent energy intake compared to
142 isoenergetic animal-based meals, largely due to this fiber-protein synergy.¹⁶ Additionally, certain
143 antinutritional compounds like lectins and trypsin inhibitors may stimulate CCK secretion though
144 their retention must be balanced against their potential to limit the bioavailability of amino acids
145 needed for muscle protein synthesis. Optimized processing, such as the combination of pea protein
146 and fiber in extruded cereals, can effectively manage glycemic and insulinemic responses while
147 preserving the satiety-enhancing components of the matrix.¹⁷

148 In short, plant proteins facilitate weight management through a multi-pathway approach
149 involving the regulation of energy intake via acute satiety signaling and the support of metabolic
150 health through muscle mass preservation (**Figure 1**). The existing evidence highlights a complex
151 relationship between internal satiety signals and actual eating behavior, which suggests that future
152 weight management strategies should move beyond acute hormonal responses. A critical area for
153 advancement lies in optimizing food processing techniques to balance protein digestibility with
154 the retention of bioactive matrix components like dietary fiber and the elimination of antinutrients,
155 particularly those that reduce the digestibility of plant protein. By tailoring the physical structure
156 of plant-based foods to prolong gastric retention or modulate nutrient release, it may be possible



157 to develop functional plant protein-based foods that provide more sustained appetite suppression.
158 Furthermore, integrating these mechanistic insights into long-term dietary interventions will be
159 essential to validate the efficacy of plant proteins in achieving sustainable weight loss and
160 improving body composition in diverse populations. Understanding these integrated relationships
161 is fundamental for the rational design of next-generation plant protein-based products that can
162 effectively address the global challenges of obesity.

163 **3. Lipid metabolism**

164 Lipid metabolism encompasses the complex processes governing the digestion, absorption,
165 transport, and utilization of fats within the body. Plant proteins influence these pathways through
166 a dual mechanism involving the modulation of initial lipid bioaccessibility in the gastrointestinal
167 tract and the direct biochemical regulation of systemic lipid synthesis and catabolism.¹⁸ These
168 complementary pathways, supported by principles of food structure science and molecular biology,
169 position plant protein consumption as a key dietary intervention for improving lipid profiles and
170 metabolic health. The effects of different plant protein sources and forms on lipid metabolism
171 together with their proposed mechanisms and experimental evidence are summarized in **Table 1**.

172



173 Table 1. Effects of plant proteins and their derived signals on lipid metabolism

Plant protein source	Form	Evidence types	Key lipid metabolic pathway	Lipid outcome	Ref
Pea and lupin protein	Emulsion-stabilizing proteins	In vitro digestion model	Protein-stabilized interfacial layers hinder lipase adsorption and lipid hydrolysis	Decreased lipid digestibility and bioaccessibility	18
Soy protein	Intact protein isolate	Meta-analysis of 46 RCTs in adults	Increased bile acid excretion, reduced cholesterol absorption, altered hepatic cholesterol metabolism	Decreased LDL-C and total cholesterol	25
Chickpea protein; Lentil protein	Purified intact protein	Wistar rats (28-day feeding)	Reduced hepatic TG synthesis and VLDL export; decreased adipose tissue LPL activity; increased hepatic lipase activity	Decreased plasma TG, VLDL particle number and TG content, liver TG and cholesterol	20
Soy protein	Intact dietary proteins	High-fat diet-fed mice	Regulation of AMPK/mTOR signaling and gut microbiota-lipid metabolism interactions	Improved lipid profile and insulin sensitivity	33
Red bean protein concentrate	Protein concentrate (with associated phytochemicals)	In vitro antioxidant assays	Antioxidant activity limiting oxidative damage to lipids	Decreased lipid peroxidation	27
Rapeseed meal protein	Enzymatic hydrolysates (bioactive peptides)	In vitro antioxidant and lipid oxidation models	Metal chelation and radical scavenging by low-molecular-weight peptides	Decreased lipid oxidation in model systems	23
Rapeseed protein	Purified bioactive peptide (EFLELL)	Cell-based assays + molecular docking	Modulation of LDLR-PCSK9 signaling; inhibition of PCSK9-LDLR interaction	Decreased TC, TG, and LDL-C	21
Pea protein	Protein hydrolysate	GDM mouse model	Inhibition of PI3K/AKT/mTOR/PPAR γ signaling; restoration of PC, PE, and FAHFA species	Decreased TG, TC, LDL-C, hepatic and placental lipid accumulation; improved placental lipid profile	17
Pea protein	Albumin	OA-induced LO2 hepatocyte model	Inhibition of lipid synthesis; activation of triglyceride catabolism and fatty acid oxidation pathways	Decreased intracellular TG and TC, lipid droplet accumulation, ALT, AST, MDA; improved GSH-Px	26

174

175 Among them, a primary pathway is the ability of plant proteins to physically govern lipid

176 digestion and absorption. Their functionality as emulsifiers and gelation agents within the food

177 matrix actively determines lipid bioaccessibility including the fraction of digested lipids available



178 for intestinal uptake. For instance, Keuleyan et al. found that lipid bioaccessibility was
179 significantly lower in emulsions stabilized with lupin protein ingredients compared to pea protein
180 isolates, while their lipolysis rates were similar.¹⁹ Beyond acting as a physical barrier, the
181 molecular interactions between plant proteins and lipid species further dictate metabolic outcomes
182 through the binding of cholesterol and bile acids. Mechanistic disparities are also evident among
183 cereal proteins. While wheat proteins are primarily valued for their techno-functional roles in food
184 matrices, oat-derived protein hydrolysates exhibit a significant biochemical capacity to bind bile
185 acids such as taurocholate, with values reaching 46.3% following digestion. This sequestration of
186 bile acids disrupts enterohepatic circulation and promotes hepatic cholesterol conversion, a
187 mechanism that is far more pronounced in oat than in traditional wheat-based proteins.²⁰ By
188 promoting the fecal excretion of these bile acids, plant proteins disrupted enterohepatic circulation
189 and stimulated the hepatic conversion of cholesterol into new bile acids.

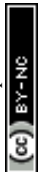
190 Furthermore, plant proteins provide essential protection against lipid oxidation during the
191 complex process of digestion. The gastric environment can promote the formation of pro-oxidant
192 species that lead to the generation of toxic lipid hydroperoxides and aldehydes. Many plant-derived
193 proteins and their hydrolyzed peptides possess inherent antioxidant properties such as radical
194 scavenging and metal chelating activities.^{21, 22} Lucrecia et al. demonstrates that while intact red
195 bean protein concentrate showed limited activity, their gastric and duodenal digests significantly
196 inhibited lipid peroxidation. Specifically, red bean protein concentrate digests was able to inhibit
197 lipid oxidation by up to 93% in vitro and maintained high efficacy in vivo using zebrafish models.²³
198 Similar protective mechanisms have been reported for rapeseed meal protein hydrolysates
199 produced by controlled enzymatic proteolysis, which exhibited strong reducing power and
200 pronounced metal-chelating activity, particularly in Prolyve-derived (*Bacillus licheniformis*)



201 proteinases) peptide fractions, thereby effectively limiting lipid oxidation in model systems.²⁴
202 These findings were also complemented by studies on oat bran protein hydrolysates that similarly
203 protected human low-density lipoprotein (LDL) against copper-mediated lipid oxidation by
204 reducing the concentration of lipid hydroperoxides.²⁰

205 Beyond intestinal protection, plant proteins can be engineered into delivery systems that
206 temporally control lipid release. For example, Browning et al. have developed stable
207 microcapsules from pea protein isolate that protect lipid cargo (e.g., oils) in gastric conditions and
208 release it in the intestine.²⁵ This strategy can delay and attenuate postprandial lipid absorption to
209 smooth the metabolic load. By reducing the rate and extent of lipid absorption, plant protein-based
210 matrices can lower chylomicron output and alleviate the postprandial lipemic burden on the liver.
211 The consistent reduction in LDL cholesterol observed in human trials by substituting animal
212 protein with plant protein is congruent with a mechanism that reduces the efficient absorption of
213 dietary cholesterol and saturated fats.^{26, 27}

214 In addition to their intrinsic nutritional value, plant proteins exhibit important synergistic
215 interactions with unsaturated fatty acids (UFAs), particularly in the regulation of lipid digestion
216 and postprandial lipid metabolism. Plant proteins, especially in their native or mildly processed
217 forms, can act as natural emulsifiers and adsorb at the oil-water interface to form viscoelastic
218 interfacial layers around lipid droplets. These protein-stabilized interfaces create steric and
219 electrostatic barriers that hinder the adsorption and activity of pancreatic lipase and bile salts,
220 thereby slowing the hydrolysis of triglycerides and reducing lipid bioaccessibility.^{28, 29} This
221 interfacial modulation mechanism leads to a more gradual release of free fatty acids during
222 digestion, which may contribute to the attenuation of postprandial lipemia and improved lipid
223 metabolic responses. In addition, the structural properties of plant proteins, including their



224 aggregation state, flexibility, and surface hydrophobicity, can further influence emulsion stability
225 and digestion kinetics, highlighting the importance of protein physicochemical characteristics in
226 determining lipid digestion behavior

227 Parallel to physical modulation in the gut, plant proteins and their derivatives enact direct
228 biochemical effects on endogenous lipid metabolism, primarily in the liver. Upon digestion, plant
229 proteins release bioactive peptides that function as endogenous metabolic regulators. A well-
230 documented mechanism is the inhibition of hepatic 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)
231 reductase, the rate-limiting enzyme in cholesterol synthesis, by peptides derived from soy, quinoa,
232 and beans.^{30,31} Concurrently, certain peptides have been shown to upregulate hepatic LDL receptor
233 expression, enhancing the clearance of circulating LDL cholesterol.²⁶ These peptides thus operate
234 dually, i.e, suppressing *de novo* cholesterol production while accelerating its removal.

235 The benefits of plant proteins are further amplified by the gut microbiome through the gut-
236 liver axis. Fermentation of co-existing dietary fiber produces short-chain fatty acids (SCFAs) like
237 propionate, which function as signaling molecules. In hepatic cells, SCFAs activate the AMP-
238 activated protein kinase (AMPK) pathway. This leads to the upregulation of peroxisome
239 proliferator-activated receptor alpha (PPAR α), a master regulator that enhances fatty acid β -
240 oxidation and suppresses lipogenesis.³² This gut-liver axis represents a critical indirect pathway
241 for plant proteins to improve lipid homeostasis. For instance, Ji and coworkers found that
242 supplementation with soy protein isolate (SPI) in mice fed a high-fat diet not only activated hepatic
243 AMPK signaling but also improved systemic insulin sensitivity and lipid metabolism. Furthermore,
244 SPI positively remodeled the gut microbiota by increasing its diversity and reducing potentially
245 harmful genera, which demonstrated how a single plant protein intervention can simultaneously



246 engage both the hepatic AMPK pathway and the gut microbial ecosystem to restore metabolic
247 homeostasis.³³

248 Recent advances in lipidomics have provided deeper insight into how dietary patterns
249 including the consumption of plant proteins modulate lipid metabolism at the molecular level. A
250 large-scale lipidomic study in 2,860 adults demonstrated that higher protein intake was inversely
251 associated with multiple sphingolipid subclasses, including ceramides, hexosylceramides, and
252 sphingomyelins. However, the opposite trend was observed in a higher saturated fat intake which
253 increased several sphingolipid species and the associated cardiometabolic risk.³⁴ These findings
254 imply that plant protein-rich diets may induce favorable modifications in both classical lipid
255 markers and deeper molecular lipid species. However, despite these promising associations,
256 current understanding remains constrained by several key limitations. In particular, interventional
257 studies combining plant protein dietary shifts with comprehensive lipidomics profiling remain
258 scarce, and most mechanistic evidence concerning bioactive peptides and gut microbiota-derived
259 metabolites (e.g., SCFAs) is still derived from in vitro animal models, with human data and clear
260 quantification of individual variability in response notably lacking. Future research must therefore
261 prioritize well-controlled human interventions that integrate multi-omics approaches to bridge
262 these gaps, confirm causality, and translate the compelling mechanistic insights into validated,
263 personalized plant protein based dietary strategies for effective lipid management.⁴

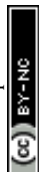
264 **4. Gut health**

265 The human gut microbiota is a highly diverse and dynamic ecosystem that plays an essential
266 role in host digestion, immune regulation, and metabolic homeostasis. Plant proteins possess a
267 distinctive capacity to interact with this microbial community, which is partly due to their generally
268 lower digestibility in the small intestine compared to animal-derived proteins. Consequently, a



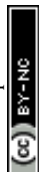
269 greater proportion of undigested proteins and peptides reaches the colon, where they serve as
270 substrates for microbial fermentation.³⁵ The extent of this interaction is shaped by the intrinsic
271 structural traits of plant protein source, such as the high hydrophobicity and trypsin inhibitor
272 content found in soy protein.

273 To improve the gastrointestinal fate of plant proteins and modulate their impact on gut health,
274 a variety of processing strategies have been developed to reduce structural barriers, inactivate anti-
275 nutritional factors, and enhance upper gastrointestinal digestibility. Thermal treatments like
276 extrusion and biological strategies such as fermentation are widely applied for this purpose.³⁶
277 Comparative studies have indicated that while fermentation primarily improves sensory profiles
278 and reduces antinutrients, its impact on digestibility can be limited compared to thermomechanical
279 methods. Specifically, high-moisture extrusion (HME) has been shown to increase the degree of
280 protein hydrolysis in sunflower-pea blends to 52.8%, significantly outperforming mild heating.
281 This is because HME's combined thermal and mechanical shear more effectively uncoils globular
282 proteins, though excessive heat may still lead to insoluble aggregates that increase the load of
283 resistant protein in the colon.³⁷ While fermentation may differ in its impact on initial hydrolysis,
284 it remains a powerful tool for improving nutritional availability. For example, solid-state
285 fermentation of red kidney beans has been shown to significantly elevate free amino acid levels
286 and increase peptide production during subsequent digestion.³⁸ A mechanistic *in vitro* study by
287 Kim et al. further demonstrated that probiotic fermentation of pea protein reduced poorly digestible
288 β -sheet structures by 53.92% and improved overall digestion by 22.50%.³⁹ Meanwhile, *in vivo*
289 evidence also aligns with these findings, as Jäger et al. reported that consuming 20 g of pea protein
290 together with five billion colony-forming units each of *Lactobacillus paracasei* LP-DG (CNCM
291 I-1572) and LPC-S01 (DSM 26760) for two weeks enhanced systemic amino acid availability,



292 with the increment for methionine, histidine, and for branched-chain amino acids being 16.3%,
293 49.2%, and 26.8%, respectively.⁴⁰ These improvements are critical because they limit the substrate
294 available for putrefactive fermentation. Unlike animal proteins, plant-based diets often feature a
295 lower ratio of sulfur-containing amino acids, which results in reduced production of hydrogen
296 sulfide. This is beneficial because high concentrations of hydrogen sulfide can impair
297 mitochondrial respiration in colonocytes and compromise the mucosal barrier. However,
298 overprocessing can lead to unintended consequences for gastrointestinal physiology. Extensive
299 heat treatment can induce the formation of advanced Maillard reaction products and insoluble
300 protein aggregates. These modifications diminish enzymatic digestibility and increase the load of
301 resistant protein substrates available for microbial proteolysis.⁴¹ Such alterations may shift colonic
302 fermentation toward pathways associated with mucosal irritation.

303 Additionally, the synergistic interaction between plant proteins and probiotics plays a pivotal
304 role in shaping the gut ecosystem. Probiotics enhance the nutritional quality of plant proteins from
305 sources such as soybean, pea, and rice by liberating bioactive peptides and diversifying microbial
306 metabolites. While fiber fermentation produces beneficial short-chain fatty acids (SCFAs), certain
307 plant proteins are rich in tryptophan that serves as a precursor for microbial-derived indoles like
308 indole-3-propionic acid (IPA). These metabolites act as signaling ligands for the aryl hydrocarbon
309 receptor (AhR) in the gut mucosa to promote immune homeostasis and strengthen the intestinal
310 barrier. This synergy is evidenced by research using aging senescence-accelerated mouse prone 8
311 (SAMP8) mouse models where a low-protein diet supplemented with soy and pea protein isolates
312 and probiotics significantly improved protein utilization and muscle strength. As reported by Han
313 et al.⁴², these functional benefits were accompanied by increased abundances of beneficial
314 bacterial taxa such as *Bifidobacterium* and *Roseburia*, along with elevated levels of butyrate and

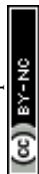


315 IPA. Importantly, these metabolic shifts were associated with reduced circulating inflammatory
316 cytokines and the modulation of immune-related genes, which highlights a functional link between
317 plant protein and probiotic co-intervention in regulating host health through the gut-muscle axis.

318 In vivo evidence further indicates that plant proteins influence colonic microbial metabolism
319 in a manner that differs from animal-derived proteins. Diets based on soybean or cottonseed
320 protein have been shown to produce significantly lower concentrations of proteolytic products like
321 ammonia compared to animal-protein diets.⁴³ This suggests that plant proteins, possibly through
322 their fiber-associated matrix and lower rates of small intestinal escape, reduce the availability of
323 undigested substrates in the hindgut and moderate microbial putrefaction. Human studies support
324 this observation, as legume-rich dietary patterns have been found to increase the abundance of
325 beneficial bacterial groups like *Bifidobacterium* and *Roseburia*. These microbial changes are often
326 accompanied by reductions in inflammatory biomarkers and improved lipid profiles.⁴⁴

327 **5. Non-communicable diseases**

328 The relationship between dietary protein sources and the development and progression of
329 non-communicable diseases (NCDs) has emerged as a critical area of nutritional epidemiology and
330 clinical research. While the fundamental role of adequate protein intake in human health is
331 undisputed, contemporary science is increasingly focusing on how the source of dietary protein
332 specifically the shift from animal-based to plant-based origins modulates disease risk through
333 distinct physiological mechanisms. This section will examine the evidence linking plant protein
334 consumption to three major NCDs: cardiovascular disease, diabetes mellitus, and chronic kidney
335 disease. The analysis will explore not only the observed epidemiological associations but also the
336 underlying molecular and metabolic pathways that explain these relationships, while
337 acknowledging areas where evidence remains limited or conflicting. The clinical efficacy of plant



338 proteins is highly dependent on tailored dosage strategies that account for the recipient's life stage
 339 and health status. As summarized in Table 2, these recommendations range from general metabolic
 340 support in healthy adults to high-purity protein-probiotic co-interventions for the elderly, and
 341 stage-specific protein source substitution for patients with chronic diseases.

342 Table 2. Summary of plant protein application evidence and dosage strategies across diverse
 343 populations.

Category	Target Group/Stage	Evidence-Based Dosage/Strategy	Key Clinical Outcome	Ref
Age Groups	General Healthy Adults	1.2-1.6 g/kg body weight/day	Maintain metabolic homeostasis and tissue repair	1
	Elderly/Sarcopenia	20 g pea protein + probiotics (e.g., <i>L.</i> <i>paracasei</i>)	Improved protein utilization, AA availability, and muscle strength	40, 42
Physiological States	Weight Management (Satiety)	50 g soy protein dose or high- protein meals (25% energy)	Increased satiety perception and reduced subsequent energy intake	10, 11
	Cardiovascular Health	≥25 g/day soy protein	Significant reduction in systolic and diastolic blood pressure	49
Disease Stages	Diabetes (T2DM Prevention)	Replace 1 daily serving of red meat with legumes/nuts	11%-18% reduction in T2DM risk; improved insulin sensitivity	61, 63

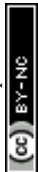


Early-Stage CKD (Stages 3-4)	Replace animal protein with 70% plant-derived protein	Slower eGFR decline, reduced proteinuria, and lower phosphorus load	73
Advanced CKD/Dialysis	Restricted total protein (0.6-0.8 g/kg) with high plant protein ratio	Attenuated generation of uremic toxins and reduced multi-organ burden	69, 72, 75

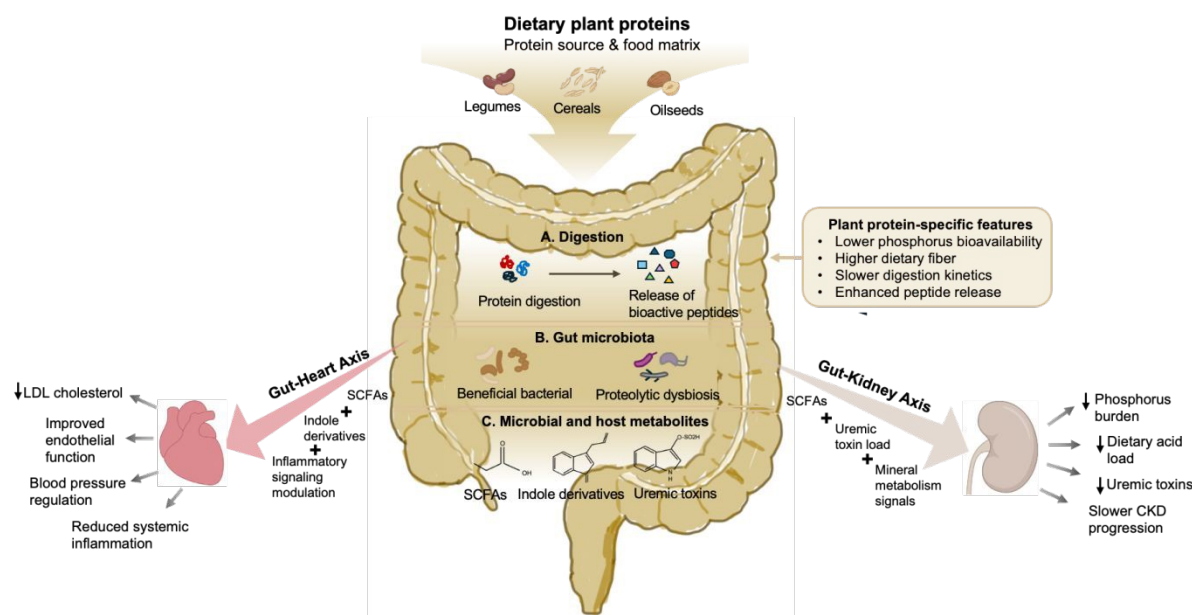
344

345 **5.1 Cardiovascular disease (CVD)**

346 As summarized in Figure 2, the cardioprotective efficacy of plant proteins is primarily
 347 mediated through three interconnected mechanisms: lipid profile optimization, blood pressure
 348 regulation, and anti-inflammatory signaling. Among these, the lipid-modifying properties of
 349 specific plant proteins have been most extensively documented. A comprehensive meta-analysis
 350 of 112 randomized controlled trials demonstrated that the isocaloric substitution of plant protein
 351 for animal protein significantly reduced established lipid targets for cardiovascular risk, including
 352 low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-
 353 C), and apolipoprotein B (ApoB).⁴⁵ Among various plant proteins, soy protein has been the most
 354 intensively studied. The bioactivity is largely attributed to globulin fractions, particularly β -
 355 conglycinin (7S) and glycinin (11S). These components are thought to upregulate hepatic LDL
 356 receptors, thereby accelerating the clearance of circulating LDL-C.⁴⁶ Notably, the efficacy of these
 357 plant proteins is also influenced by their genetic background and subunit composition. For instance,
 358 soy protein isolates (SPIs) rich in the 7S fraction, such as the 7S ($\alpha'+\alpha$)-null genotype, exhibited
 359 superior potency in elevating HDL-C levels in hypercholesterolemic models.⁴⁷ It is noteworthy



360 that the cardiovascular benefits of the soy matrix are augmented by co-occurring bioactive
 361 compounds. Isoflavones, in particular, appear to act synergistically with the soy protein fractions
 362 to modulate lipid metabolism and further improve total cholesterol profiles.⁴⁸



363
 364 Figure 2. Mechanistic overview of plant protein mediated gut-heart-kidney axis interactions

365
 366 In addition to lipid metabolism, plant-derived proteins exhibit significant vasoprotective
 367 potential through the regulation of blood pressure. Clinical meta-analyses indicate that soy protein
 368 supplementation (≥ 25 g/day) effectively reduced both systolic and diastolic blood pressure, an
 369 effect partially attributed to the vasodilatory properties of isoflavones.⁴⁹ Beyond soy, dietary pulses
 370 such as lentils and chickpeas also confer beneficial effects on vascular function and pressure
 371 regulation, suggesting that antihypertensive properties are a shared attribute among diverse legume
 372 species.⁵⁰ Recent advancements in bioactive peptide research have further elucidated the molecular
 373 mechanisms behind these observations. For instance, *Moringa oleifera* (MO) leaf protein has
 374 emerged as a potent source of antihypertensive peptides. Hydrolysates from MO leaves,
 375 specifically those with a molecular weight < 1 kDa, demonstrated the ability to exert dual inhibitory



376 effects on both angiotensin-converting enzyme (ACE) and renin in the renin-angiotensin system
377 (RAS). Identified peptide sequences, such as Leu-Gly-Phe-Phe (LGF) and Gly-Leu-Phe-Phe
378 (GLFF), not only significantly lowered blood pressure in spontaneously hypertensive rats (SHRs)
379 but also demonstrated remarkable stability against gastrointestinal digestion.⁵¹ Despite these
380 promising molecular findings, the application of leafy biomass proteins is currently constrained
381 by low bioaccessibility and a lack of long-term human intervention studies to validate their
382 efficacy and safety. Another broader meta-analysis reported that while substituting protein for
383 carbohydrates lowers blood pressure, the effects of plant and animal protein were broadly similar,
384 suggesting that the benefit in such comparisons may be partly attributed to protein per se, and the
385 definitive superiority of plant protein for blood pressure requires further confirmation.⁵²

386 Plant proteins also significantly attenuate systemic chronic inflammation, a pathological
387 hallmark of CVD. This anti-inflammatory efficacy is believed to arise from a synergistic interplay
388 between bioactive peptides and co-passengers within the plant matrix. At the molecular level, soy-
389 derived tripeptides such as Leu-Ser-Trp (LSW) have been shown to suppress vascular
390 inflammation by downregulating COX-2 and angiotensin II Type 1 receptor (AT1R) expression
391 via the SRC/ERK signaling pathway.⁵³ This protective effect extends to systemic markers. For
392 instance, chickpea protein hydrolysates was reported to not only reduce C-reactive protein in
393 hypercholesterolemic models but also uniquely enhance the antioxidant capacity of HDL,
394 outperforming animal-derived proteins like casein.⁵⁴ Furthermore, the matrix effect of plant-based
395 foods integrates the actions of associated bioactive constituents. The intrinsic isoflavones and other
396 polyphenols in plant protein isolates were shown to interfere with pro-inflammatory cytokine
397 cascades, thereby stabilizing the vasculature.⁵⁵ Crucially, the inclusion of dietary fiber facilitates
398 a gut-heart axis mechanism. A study reported that supplementation with soy-based matrices

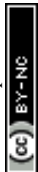


399 restored gut microbiota eubiosis by increasing the production of SCFAs like butyrate. This, in turn,
400 upregulated colonic anti-inflammatory markers (e.g., IL-10, Foxp3) and reinforced intestinal
401 barrier integrity via zonula occludens protein-1 (ZO-1) and membrane linker protein occludin,
402 preventing the translocation of pro-inflammatory endotoxins into the circulation.⁵⁶

403 Despite the robust evidence supporting the cardiometabolic benefits of plant proteins, clinical
404 efficacy exhibits significant heterogeneity depending on intervention parameters. For instance, a
405 rigorous six-month trial in postmenopausal women with prediabetes found that daily
406 supplementation with 15 g of soy protein (plus 100 mg of isoflavones) failed to significantly alter
407 inflammatory or lipid markers compared to a milk protein control.⁵⁷ Such discrepancies underscore
408 that the efficacy of plant proteins is modulated by a complex constellation of factors, including
409 participant baseline metabolic status, intervention dosage, duration, and the specific dietary matrix
410 used as a realized when these variables are optimized to ensure meaningful dietary substitution.
411 Furthermore, emerging evidence suggests that the benefits of plant proteins may extend to
412 improving the functional quality of protective molecules. A notable example is the effect of rice
413 endosperm protein which enhanced the intrinsic anti-inflammatory capacity of high-density
414 lipoprotein (HDL) in murine models. This functional improvement in HDL was directly correlated
415 with reduced atherosclerotic lesion formation, revealing a protective pathway that complements
416 traditional lipid-lowering and anti-inflammatory mechanisms.⁵⁸

417 **5.2 Diabetes mellitus**

418 Type 2 diabetes mellitus (T2DM) is characterized by a complex interplay of insulin resistance,
419 β -cell dysfunction, and chronic systemic inflammation. Plant protein-rich foods, including
420 legumes, cereals, nuts, and oilseeds, differ from animal protein foods in nutrient matrix, typically
421 providing more unsaturated fatty acids, polyphenols, and dietary fiber when consumed in their



422 minimally processed form.⁵⁹ Prospective cohort analyses suggest that replacing red and processed
423 meats with legumes, nuts, whole grains, or isolated plant protein reduces diabetes incidence,
424 largely through improvements in lipid profiles and reduced exposure to saturated fat, heme iron,
425 and advanced glycation end products. For example, a meta-analysis of 11 cohort studies reported
426 that higher total and animal protein intake were associated with an increased risk of T2DM,
427 whereas plant protein intake showed a neutral to protective association, particularly in women.⁶⁰
428 Specifically, modeling the replacement of one daily serving of red meat with legumes or nuts was
429 associated with an 11% to 18% reduction in T2DM risk.⁶¹

430 The amino acid composition of plant proteins may further contribute to their metabolic
431 advantages in glycemic regulation. Compared with many animal-derived proteins, plant proteins
432 generally contain lower levels of branched-chain amino acids, methionine, and aromatic amino
433 acids, which have been associated with impaired insulin sensitivity when consumed in excess.⁶² Ji
434 et al. demonstrated that soy protein isolate was more effective than whey protein isolate in reducing
435 fasting insulin concentrations and enhancing whole-body insulin sensitivity, as assessed by
436 Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), in obese and insulin-resistant
437 mouse model.⁶³ Such metabolic improvements may reflect slower gastric emptying, altered amino
438 acid absorption kinetics, and activation of nutrient-sensing pathways, which collectively enhance
439 insulin sensitivity.⁶²

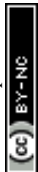
440 Beyond fundamental amino acid profiles, the digestion kinetics of plant proteins and the
441 subsequent liberation of bioactive peptides play a decisive role in glycemic regulation. Specific
442 plant-derived oligopeptides have been shown to enhance insulin signaling through the modulation
443 of PI3K-Akt signaling pathways and the attenuation of oxidative stress in insulin-sensitive tissues.
444 For instance, pea-derived peptides restored IRS-1-Akt signaling in insulin-resistant HepG2 cells,



445 while peptides from algae and chickpeas exhibited potent inhibitory activity against dipeptidyl
446 peptidase-IV (DPP-4).⁶⁴ Specifically, the identified short-chain peptides from chickpea
447 hydrolysates were the key contributors to this enzymatic inhibition, which served to prolong the
448 half-life of incretin hormones and improved postprandial glucose disposal.^{65, 66} Moreover, plant
449 proteins typically coexist with intact dietary fiber in whole-food matrices, which delays glucose
450 absorption and contributes to attenuated postprandial glycemia.⁶⁷ Nevertheless, the metabolic
451 efficacy of these plant proteins is highly sensitive to technological interventions. While
452 fermentation and controlled enzymatic hydrolysis can enhance the bioaccessibility of antioxidant
453 and anti-inflammatory fragments, excessive thermal treatments or advanced Maillard reactions
454 may impair peptide formation and reduce the overall glycemic benefits of plant proteins. These
455 observations indicate that the technological context of consumption is a critical determinant of the
456 functional properties of plant proteins in diabetes management.⁶⁸

457 **5.3 Chronic kidney disease**

458 Chronic kidney disease (CKD) is characterized by a progressive decline in glomerular
459 filtration rate and the accumulation of uremic toxins. While traditional management emphasized
460 restricted protein intake to minimize renal workload, contemporary research identifies the protein
461 source as a critical modulator of disease progression. Prospective cohort analyses revealed that
462 higher intake of plant-derived proteins, particularly as a replacement for red and processed meats,
463 was associated with a significantly slower decline in estimated glomerular filtration rate (eGFR)
464 and reduced proteinuria. A recent meta-analysis further demonstrated a consistent dose-response
465 relationship between plant-based dietary patterns and reduced CKD incidence.⁶⁹ Notably,
466 NHANES III data indicated that a higher proportion of dietary plant protein was associated with
467 lower all-cause mortality for individuals with an eGFR below 60 mL/min/1.73 m².⁷⁰



468 The modulation of the gut-heart-kidney axis is increasingly recognized as another key benefit
469 **(Figure 2)**. Plant proteins facilitate a healthier gut microbiota profile, leading to the attenuated
470 generation of gut-derived uremic toxins such as p-cresyl sulfate and indoxyl sulfate.⁷¹ Clinical
471 trials, such as the one conducted by Azadbakht et al., demonstrated that partially replacing animal
472 protein with soy protein in patients with diabetic nephropathy resulted in significant reductions in
473 proteinuria and urinary urea nitrogen. These improvements are often accompanied by optimized
474 lipid profiles and reduced markers of systemic inflammation, collectively alleviating the multi-
475 organ burden characteristic of CKD.⁷² Phosphorus bioavailability represents another critical
476 distinction between plant and animal protein sources. Phosphorus in plant-based foods is largely
477 bound to phytate, leading to substantially lower intestinal absorption compared with the highly
478 bioavailable inorganic and animal-derived phosphorus abundant in meat and processed foods. In
479 patients with stage 3-4 CKD, a controlled dietary intervention replacing animal protein with a diet
480 containing 70% plant-derived protein for four weeks significantly reduced 24-hour urinary
481 phosphorus excretion and dietary acid load without adverse effects on muscle mass or functional
482 status.⁷³

483 Nevertheless, the application of plant proteins must be tailored to the specific stage of CKD
484 and individual metabolic needs. According to the NHANES-based analyses, the association
485 between plant protein intake and renal outcomes is not linear but follows a stage-specific pattern.
486 While moderate to high plant protein ratios are favorable in non-CKD and early CKD stages, these
487 associations can become attenuated or non-significant in advanced stages. Dose-response analyses
488 even revealed U-shaped or inverted U-shaped relationships, suggesting that the optimal protein
489 balance may shift as renal function declines.⁷⁴ In early-stage CKD, whole-food plant sources like
490 legumes and whole grains provide essential fiber and a low acid load that support renal longevity.



491 For patients with advanced CKD or those requiring dialysis, practical concerns regarding
492 potassium burden and phosphorus management may necessitate more structured dietary oversight,
493 indicating that the technological form and processing of plant proteins remain critical determinants
494 of their clinical utility in end-stage renal care.⁷⁵

495 **6. Future needs**

496 Despite the accumulating evidence supporting the preventive and/or therapeutic potential of
497 plant proteins, several critical knowledge gaps must be addressed to translate these findings into
498 precise clinical guidelines. The following sections outline the essential research priorities
499 required to advance our understanding of plant protein based nutrition.

500 **6.1 Diversity and specificity of plant protein sources**

501 While plant protein intake is broadly linked to favorable outcomes, there is an urgent need to
502 disentangle the specific roles of different origins. Plant proteins are often treated as a homogeneous
503 dietary category in observational studies and dietary guidelines, despite substantial heterogeneity
504 in amino acid composition, protein structure, digestibility, and food matrix interactions across
505 different origins.⁵ Legume-derived proteins (e.g., soy, pea, lentil, chickpea), cereal proteins (e.g.,
506 wheat, rice, oat), and proteins from oilseeds or pseudocereals differ markedly in their proportions
507 of essential amino acids, sulfur-containing amino acids, and branched-chain amino acids, as well
508 as in their associations with fiber, phytate, and polyphenols. Beyond traditional crops, novel plant
509 proteins such as leafy biomass (e.g., RuBisCO from alfalfa or duckweed) represent a sustainable
510 alternative with a balanced essential amino acid profile. However, their practical application is
511 currently constrained by significant technical and sensory limitations. The intensive biorefinery
512 processes required to remove chlorophyll and phenolic compounds can lead to protein denaturation,
513 while persistent green off-notes and bitter flavors remain primary barriers to consumer



514 acceptance.⁷⁶ These intrinsic differences and technological challenges are likely to influence
515 postprandial metabolism, nitrogen utilization efficiency, acid load, and gut microbial fermentation,
516 yet remain insufficiently addressed in current research. Therefore, the extent to which observed
517 health benefits attributed to plant protein are driven by specific sources rather than plant-based
518 diets as a whole remains unclear.

519 Future research should prioritize controlled comparisons among distinct plant protein sources
520 to clarify their differential metabolic and clinical effects. While soy protein has been extensively
521 studied and often serves as a reference plant protein, its dominance in the literature may limit
522 generalizability to other increasingly consumed proteins such as pea, faba bean, lentil, and cereal-
523 derived proteins. Moreover, future studies can prioritize controlled, head-to-head comparisons of
524 major and emerging plant protein sources (e.g., legume vs. cereal vs. oilseed proteins) to delineate
525 their distinct impacts on human health. Emerging dietary patterns and food technologies have
526 rapidly expanded the use of non-soy plant proteins in both whole-food and processed formats, yet
527 long-term human intervention studies evaluating their effects on glycemic control, lipid
528 metabolism, renal function, and mineral homeostasis are scarce. Additionally, the physiological
529 effects of plant proteins are further shaped by their form of utilization, including whole-food
530 matrices, plant protein concentrates, isolates, hydrolysates, and derived bioactive peptides.
531 Processing and fractionation can markedly alter protein structure, digestion kinetics, and
532 interactions with other dietary components, thereby modulating postprandial amino acid
533 availability, lipid handling, and gut microbial responses. For example, protein isolates and
534 hydrolysates may exhibit enhanced digestibility or bioactivity compared with intact proteins, yet
535 they lack the complex food matrix present in whole legumes or cereals, which can slow digestion
536 and influence metabolic outcomes. Consequently, evidence derived from isolated or hydrolyzed

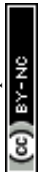


537 plant proteins may not be directly extrapolated to whole-food sources, even when derived from the
538 same origin. Distinguishing between protein source and protein form as well as understanding their
539 interaction is therefore essential for interpreting heterogeneous findings across studies and for
540 translating plant protein research into dietary recommendations.

541 **6.2 The food matrix and synergistic interactions**

542 Plant proteins are inherently consumed within complex food matrices rich in dietary fiber,
543 resistant starch, and diverse polysaccharides. These constituents can modulate nutrient absorption,
544 gastrointestinal transit, and microbial metabolism, thereby influencing the physiological effects of
545 plant proteins. A key research imperative is to move beyond studying isolated protein effects and
546 to quantify the synergistic interactions between plant proteins and these co-passengers. We must
547 elucidate how fibers from legumes, cereals, and oilseeds jointly modulate gastric emptying,
548 nutrient absorption kinetics, and gut microbial metabolism to produce the attenuated postprandial
549 glycemic responses and enhanced SCFA production observed with whole foods. Understanding
550 these matrix-driven synergies is critical to explain why health outcomes from whole plant foods
551 may not be fully replicable by isolated plant protein ingredients.

552 Plant proteins often coexist with polyphenols, flavonoids, saponins, and other secondary
553 metabolites that can further enhance metabolic and health outcomes. These bioactive
554 phytochemicals exert antioxidant and anti-inflammatory effects, potentially complementing the
555 benefits of protein-derived peptides in insulin sensitivity, lipid regulation, and renal function. For
556 example, isoflavones in soy and phenolic compounds in legumes have been reported to reduce
557 oxidative stress in vitro and in animal models, and to modulate enzymes involved in carbohydrate
558 and lipid metabolism.⁷⁷ The interaction between these phytochemicals and plant protein may
559 potentiate the formation or activity of bioactive peptides during gastrointestinal digestion,



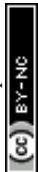
560 suggesting a cooperative effect that extends beyond the protein itself. Future research can move
561 beyond observing additive effects to mechanistically dissect these interactions and quantify the
562 relative contribution of protein versus phytochemicals to observed health outcomes in humans.

563 However, plant protein matrices are often rich in phytate, an antinutritional factor that can
564 chelate essential minerals such as iron, zinc, and calcium, thereby reducing their bioavailability.
565 This presents a potential limitation in plant protein-based diets, particularly in populations with
566 marginal micronutrient intake. To mitigate these effects, various processing strategies such as
567 fermentation, germination, enzymatic hydrolysis, and phytase treatment have been shown to
568 effectively degrade phytate and enhance mineral bioaccessibility.⁷⁸ By reducing antinutritional
569 compounds and improving peptide release, such approaches enable the concurrent delivery of
570 high-quality amino acids and functional co-factors. The efficacy of plant protein modification is
571 highly sensitive to optimized processing parameters. For HME, maintaining a moisture content of
572 60-65% and specific temperature profiles is critical to achieving a meat-like fibrillar texture
573 without inducing excessive protein cross-linking that might hinder enzyme accessibility.³⁷
574 Furthermore, processing technologies such as fermentation and extrusion exert synergistic effects
575 on the entire food matrix by modulating interactions between proteins, fibers, and phytochemicals.
576 Combining fermentation with a neutral pH shift prior to extrusion can effectively remove intensive
577 off-odors; however, the impact on the matrix integrity must be carefully managed. Research on
578 rapeseed protein indicated that fermentation-induced proteolysis can release short peptides that
579 may form complexes with fiber-derived polysaccharides and phytochemical hydrolysis products
580 (e.g., from glucosinolates), which potentially hinders the formation of the fibrous structure
581 required for meat analogues.⁷⁹ Future research can systematically establish quantitative
582 relationships between specific processing parameters (e.g., fermentation strains, enzymatic



583 hydrolysis conditions, extrusion temperature) and the resultant modifications in the food matrix.
584 Key outcomes to measure include the reduction of antinutritional factors, the preservation or
585 enhancement of bioactive phytochemicals, the improvement of protein digestibility and amino acid
586 release kinetics, and the consequent metabolic responses in vivo. This relationship among
587 processing, matrix, and function is essential for rationally designing next-generation plant-protein
588 ingredients and foods that maximize nutritional quality and deliver targeted health benefits beyond
589 basic protein supplementation.

590 Ultimately, emerging evidence has highlighted the synergistic potential of plant proteins and
591 probiotics in modulating gut health and preventing non-communicable diseases (NCDs). Within
592 the food matrix, plant protein digestion products serve as critical substrates for gut microbiota,
593 promoting the production of short-chain fatty acids (SCFAs) and beneficial metabolites like
594 indole-3-propionic acid. When combined with specific probiotic strains, these proteins enhance
595 microbial diversity and reinforce the intestinal barrier, thereby reducing systemic inflammation.⁸⁰
596 This mechanistic potential is increasingly supported by clinical application evidence. For instance,
597 a randomized clinical trial (RCT) involving 100 patients with Type 2 Diabetes Mellitus (T2DM)
598 demonstrated that a six-week intervention with soymilk and probiotics significantly improved
599 cardiovascular risk profiles-evidenced by reductions in diastolic blood pressure, triglycerides, and
600 total cholesterol-alongside improved insulin sensitivity.⁸¹ While statistical synergy compared to
601 individual components may vary across study designs, the observed metabolic improvements
602 underscore the practical efficacy of integrated dietary strategies for multi-target management of
603 chronic diseases. This perspective emphasizes that plant proteins are not merely individual
604 nutrients but integral modulators within a complex diet-microbiota-host interaction network,
605 where the food matrix ultimately governs the physiological outcome.⁸²



606 **6.3 Peptidomics and gastrointestinal digestion as a functional gateway**

607 Gastrointestinal digestion is increasingly recognized not merely as a degradative process, but
608 as a critical phase for the generation and functional exposure of bioactive peptides from dietary
609 proteins. Proteolysis by gastric and pancreatic enzymes can release encrypted peptide sequences
610 that are inactive within the native protein structure but acquire biological activity upon digestion.
611 A comprehensive review has demonstrated that digestive conditions including enzyme specificity,
612 pH gradients, and food matrix interactions strongly determined the peptide profiles generated from
613 food proteins and, consequently, their physiological relevance.⁸³ From this perspective, protein
614 digestibility does not solely dictate amino acid availability, but also governs the emergence of
615 peptide-mediated regulatory effects on host metabolism.

616 Accumulating experimental evidence has indicated that plant protein-derived peptides can
617 directly modulate glucose homeostasis through effects on insulin signaling and carbohydrate
618 metabolism. In cellular models of insulin resistance, oligopeptides derived from pea protein
619 digestion have been shown to restore IRS-1 and Akt phosphorylation, suppress oxidative stress-
620 related pathways, and enhance glucose uptake, thereby improving insulin responsiveness in
621 hepatocytes.⁶⁴ Similar mechanisms have been reported for peptides released from soy and lupin
622 proteins, which influenced PI3K-Akt signaling cascades and attenuated stress-activated kinases
623 implicated in insulin resistance. However, most available evidence is derived from simulated
624 digestion systems and in vitro cellular models, and key uncertainties remain regarding peptide
625 stability, intestinal permeability, and effective concentrations under physiological dietary
626 conditions. Addressing these gaps will require integrated approaches combining dynamic
627 digestion models, intestinal transport studies, and well-designed human interventions to establish
628 the true relevance of digestion-derived plant protein peptides for chronic disease prevention.



629 The kinetics of peptide release and persistence during digestion further distinguish plant
630 proteins from many animal-derived counterparts. The relatively slower digestion rates and
631 heterogeneous protein structures of legumes and cereals promote a more gradual liberation of
632 peptides and amino acids, which may favor sustained metabolic signaling rather than rapid
633 postprandial excursions. Importantly, food processing strategies strongly influence these outcomes.
634 Fermentation and controlled enzymatic hydrolysis can enhance the generation of functional
635 peptides with antioxidant, enzyme-inhibitory, or anti-inflammatory properties, whereas excessive
636 thermal treatment may impair peptide release or reduce bioactivity. Future studies should move
637 beyond identifying these inhibitory effects and instead focus on quantifying how specific
638 processing parameters determine the structural integrity and physiological potency of plant-
639 derived peptides.

640 Current evidence supports a conceptual framework in which gastrointestinal digestion serves
641 as a functional gateway that transforms plant proteins into a diverse repertoire of bioactive peptides
642 capable of modulating host metabolic pathways. Elucidating the stability, absorption, and target
643 specificity of these peptides in vivo remains an important challenge, particularly in distinguishing
644 direct peptide effects from secondary metabolic adaptations. Nevertheless, advances in
645 peptidomics and digestion models continue to strengthen the link between plant protein digestion
646 and peptide-mediated regulation of glucose metabolism and metabolic health.

647 7. Conclusions

648 Plant proteins represent more than mere alternative dietary protein sources, as they exert
649 multifaceted effects on human health through mechanisms that extend far beyond protein quantity
650 and basic amino acid composition. Evidence synthesized in this review indicates that plant proteins
651 influence satiety regulation, lipid metabolism, and gut health, while also modulating the risk and



652 progression of major non-communicable diseases, including cardiovascular disease, diabetes
653 mellitus, and chronic kidney disease. These health outcomes are primarily driven by the integrated
654 effects of digestion kinetics, food matrix interactions, and the presence of bioactive compounds.
655 Importantly, the physiological impact of plant protein intake is highly context-dependent, being
656 shaped by the specific protein source, the methods of processing, and co-existing constituents such
657 as fiber and phytochemicals. Emerging data further suggest that peptides and microbial metabolites
658 derived from plant proteins can directly regulate host metabolic, inflammatory, and immune
659 pathways, highlighting mechanisms that are distinct from those traditionally associated with
660 animal proteins. Despite growing interest, comparative evidence across diverse plant protein
661 sources remains limited, and long-term human intervention studies are essential to clarify source-
662 specific efficacy as well as dose and response relationships across different disease stages.
663 Addressing these gaps will be critical for translating these mechanistic insights into practical
664 dietary recommendations and for guiding the rational development of plant protein based foods
665 with targeted health functions.

666 **Conflicts of interest**

667 There are no conflicts of interest to declare

668 **Author contributions**

669 Kun Gao: conceptualization, writing – original draft. Shiyu Zhou: writing – review &
670 editing. Jiajia Rao: writing – review & editing. Bingcan Chen: conceptualization, project
671 administration, funding acquisition, writing – review & editing.

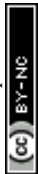
672 **Acknowledgment**

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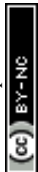
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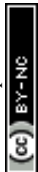
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Data availability

All data supporting this systematic review were extracted from previous publications and are available within this review.

