Phaseolus vulgaris L. prevent Cardiovascular Diseases

Subjects: Chemistry, Medicinal
Contributor: Eduardo Fuentes

The common bean (Phaseolus vulgaris L.) is known as a “new world crop”; it originated 7000 years ago in two different parts of the North and South American continents. Common beans have been highlighted as an almost perfect food due to their high content of protein, fiber, prebiotics, vitamins, and chemically diverse micronutrient composition. They have been shown to protect against oxidative stress, CVD, diabetes mellitus, metabolic syndrome, and many types of cancer. Many compounds have been identified in P. vulgaris, such as phenolic acids (chlorogenic acid, syringic acid, caffeic acid), flavonoids (kaempferol, pelargonidin, cyanidin, delphinidin), sugars, fatty acids, and tocopherols, among others.

cardiovascular diseases Phaseolus vulgaris L.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in modern societies [1] and has a substantial economic impact [2]. CVD claimed more than 10 million lives in the last 18 years [3]. Conversely, many people suffer disability after suffering cardiovascular events [4]. Ninety percent of CVD deaths are attributed to conventional cardiovascular risk factors (CVRF) [5][6], which increase the probability of suffering from CVD [7]. There are non-modifiable CVRFs such as age and genetic predisposition [8][9]. Conversely, there are modifiable CVRFs: smoking, dyslipidemia, arterial hypertension, diabetes, physical inactivity, and overweight/obesity [5][6].

Platelets are considered the main pathological risk factors for CVD, such as coronary artery disease and atherosclerosis [1]. They are known for their fundamental contributions to thrombosis and hemostasis [10][11]. Platelet activation plays a fundamental role in the development of arterial thrombosis, for which the control of platelet function is essential for the prevention of thrombotic events [12].

Diet and lifestyle are modifiable risk factors that can have a significant impact on the probability that an individual develops different diseases [13][14][15].

Nutritional status is an important factor in preparing the immune system to fight infection or prevent non-communicable diseases [13][16]. Diet can have beneficial effects on several CVD risk factors [2], due to its cardioprotective and antiplatelet effects in the primary and secondary prevention of CVD [1]. Certain components of the diet with antiplatelet activity can reduce blood platelet activation and have an important influence on the treatment of cardiovascular events [2]. It has been described that there is an inverse association between antioxidants from the diet and the development of thrombosis and other coronary events [12][17][18].

Many foods are considered functional because they provide nutrients and energy to support daily life [19]. Grain legumes contain high amounts of protein, minerals, and vitamins and play an important role in both agricultural systems and the human diet, mainly in developing countries [20][21]. Out of 13,000 species, only between 10 to 12 play a relevant role today, either for application in the food industry or other commercial purposes [22][23]. Among them, we can mention common beans (*Phaseolus vulgaris*), chickpeas (*Cicer arientinum* L.), lentils (*Lens esculenta*), peas (*Pisum sativum*), and broad beans (*Vicia faba*) [21].

Grain legumes are a considerable source of nutrients and have also been referred to as the meat of the poor [24], because of their importance for consumption in third world, countries where malnutrition is a relevant nutritional problem [25][26]. In general, beans are recognized as a good source of protein, 2–3 times greater than that of cereal grains [26][27]. In ancient times, protein of animal origin was consumed mainly. Recently, there is a trend toward a Mediterranean diet, which includes foods of plant origin rich in nutrients that help reduce cholesterol levels in the population, among other health benefits [1].

2. *Phaseolus vulgaris* L.

The common bean (*Phaseolus vulgaris* L.) is known as a “new world crop”; it originated 7000 years ago in two different parts of the North and South American continents [19][28][29]

It belongs to the genus *Phaseolus*, family Leguminosae, subfamily *Papilionoideae*, tribe *Phaseoleae*, subtribe *Phaseolinae*; it is the legume species with the highest distribution and consumption of genus *Phaseolus*, which comprises about 70 species [29]. It has five cultivars domesticated in the pre-Columbian era, domesticated species: common bean (*Phaseolus vulgaris* L.), lima bean (*P. lunatus* L.), red bean (*Phaseolus coccineus* L.), tepary bean (*P. acutifolius Gray A*.), and beans (*P. polyanthus Greenman*), which present different adaptations and reproductive systems: mesic and temperate, predominantly self-pollinated [29][30].

Phaseolus vulgaris L. represents more than 90% of the crop grown in the world [29][31]. It is considered a non-centric crop with at least two domestication centers [32] and wide geographic distribution of its wild relatives in Central and South America. This crop was domesticated from wild *Phaseolus vulgaris* L., an indeterminate viniferous plant, distributed from Mexico to Argentina, mainly in mid-altitude neotropical and subtropical regions [33]. This species is an important food for rural and urban populations, mainly in Latin America and East Africa, although its demand has currently increased in developed countries, where populations are worrying about maintaining healthier diets [32]. *Phaseolus vulgaris* L., compared to other food crops, shows great diversity in terms of growth habits, seed characteristics (size, shape, and color), maturation times, and adaptation [34].

The common bean is the most important legume in the world for both human consumption and animal feed [30]. Its consumption is aimed especially at low-income people [25]. In areas such as Mexico, Central, and South America, and African countries, there is a high consumption and are considered as staple foods, considering a per capita intake of up to 40 kg per year [26][35][36]. The leading countries in the production of these legumes are Latin America and sub-Saharan Africa, where three-quarters of this crop is grown, with a production of around 12 million metric tons per year [20][37]. The forms of consumption are varied; consumers of beans from different countries and regions, even within the same country, show different predilections according to the size, shape, and color of the seed, as well as cooking time, the appearance of the broth and shape of storage [38][39].

Phaseolus vulgaris L. is consumed mainly by its dry grains (ripe), peel beans (seeds in physiological maturity), and green pods [30][33]. Beans are not only used as a dry grain, green beans are consumed as vegetables [29]. The seeds can be used in multiple ways, such as whole unprocessed seeds, as part of mixes, canned goods, or as a substitute for gluten-free wheat flour [19]. The United Nations for Food and Agriculture (FAO) in 2016 reported world production of a dry grain of 26.8 million tons, while the production as vegetable or green bean was 23.5 million tons. The most important classes of dried beans include green beans [26], red kidney beans [40], black beans [41], beans Mexican [42], pinto beans, tirage beans [43], great northern beans, navy beans, and pink beans [26][36].

Subtypes of Bean in Chile

Despite the nutritional value of beans and their consumption in Chile, there are few studies of these crops, which date back to before 2000. Food entities recommend this product as a component of a safe diet. Several cultivars are spread and consumed throughout Chile, achieving a high impact on the national diet [21]. The consumption of beans in Chile is under 1.5 kg per capita/year [44], in comparison with the 10 to 17 kg per capita/year consumed in Central American countries, and more than 50 kg per capita in some African countries [45].

The common bean germplasm collected in Chile has been classified as races Chile, Nueva Granada, Peru, Durango, and Mesoamerica, with the only exception to the race Jalisco. The Chilean strain has distinguished itself as an important source of genetic diversity [46]. This situation could be associated with commercial reasons and mainly due to the excellent adaptation of bean species to Chilean agro-climatic conditions. The current bean collection in Chile consists of 1110 accessions [38].

In most Chilean markets, the most consumed dried beans are Tortola and Coscorrón [47]. In some specific rural areas other crops, Manteca, Sapito, and Cuyano, are also consumed regularly [48]. There are other types consumed on a smaller scale, such as “bayos” and “sulfur”, all of a single seed color, but it is also common to find grains of two or more colors, such as “strawberries”, “araucano” and “sapito”, among others [49]. Dry grain preferences in Chile are directed mainly to the texture of the cooked grain.

The Chilean race has been characterized as a sub-center of genetic diversity. A distribution analysis comprised 1239 accessions that evaluated the genetic diversity present in 11 morphological characters. Great growth variability was evidenced (leaf, flower color from white to purple, presence of all types of bracteoles, diversity of shape, size, and color of pods with dorsal or central apex). The seed showed variations in size (small to large), shape (round to elongated), and great variation in the primary color or their combination. These results were useful for the genetic improvement of “tórtola” and “coscorrón” types [49]. A recent study suggests that the Chile race would be the oldest reservoir of genetic diversity in the Andean pool, making this germplasm a relevant genetic resource [50].

There is little information on the content of minerals, flavonoids, phenolic acids, total phenols, tannins, cooking quality, and antioxidant capacity of common beans of the Chile breed [38]. A study carried out by Paredes et al., 2009, evaluated the macro and micronutrient variability of a representative sample of beans from a Chilean breed collection, comparing them with representatives of other breeds. The results showed the existence of a wide variability for some macro and micronutrients, such as N, Fe, and Zn. The protein content ranged from 183.5 to 259.7 mg kg^{-1}, Fe from 68.9 to 152.4 mg kg^{-1}, and Zn from 27.9 to 40.7 mg kg^{-1}. The bean genotypes of the Chile breed showed a good level of protein, Fe, and Zn; they did not show significant differences with the genotypes of other breeds [38]. This study allowed the selection of outstanding crops within the Chilean breeds studied, also allowing to improve current crops.

The National Institute of Agricultural Research (INIA) some years ago evaluated the proximal chemical composition and the biological quality of the protein of five new cultivars in comparison with two traditional cultivars of *Phaseolus vulgaris* L. The beans provided a large fraction of proteins and other nutrients. Dried beans also stood out for the nutritional quality of their protein, carbohydrates, minerals, and dietary fiber [21].

3. Role of Beans in CVD

3.1. Effect on Hemostasis and Platelet Aggregation

The complex pathophysiological process involved in CVD includes the participation of platelets; these have a main role during thrombosis and progression of atherosclerosis [51]. Food supplements and/or nutraceuticals have become attractive alternatives to reduce cardiovascular events [52].

The methanolic extract of *Phaseolus vulgaris* L. had been considered relevant by its antiplatelet effect, especially the ability to suppress platelet secretion, using the proposed mechanism of protein kinase A (PKA) modulation and the inhibition of AKT phosphorylation [53].

It is hypothesized that some flavonoids (kaempferol, epicatechin, delphinidin, cyanidin) can inhibit the platelet function by suppressing the platelet aggregation, calcium mobilization, integrin modulation, granule secretion, and thrombus formation, using as an example the pharmacological action of nobiletin [54].

Furthermore, other proteins can increase the activation of platelets, as is the case of lectins; these are proteins sometimes referred to as an antinutrient for decreasing the body’s ability to absorb nutrients, but this review will be focusing on the lectins-induced stimulation of fresh platelets [55].

These lectins have shown effect through phospholipase C (PLC) ɣ 2 activations, using the Src/Syk and PI3K/BTK pathways, but also an increase in the reactive oxygen species (ROS), as well as superoxide anion formation and lipid peroxidation by working as an uncoupling agent with the consequent increase in oxygen consumption and decrease in adenosine triphosphate (ATP) formation [56][57]. This activation was completely inhibited by the use of penicillin G (12.5 mM) and cephalothin (12.5 mM) [58].

Another interesting discovery is the *Phaseolus vulgaris* L. agglutinin production of nitric oxide (NO), regulated by the Ca^{2+}/calmodulin kinase/AMPK pathway in a time and dose-dependent manner. This process is dependent on the eNOS phosphorylation involving the eNOS/NO/cGMP/PKG pathway [56][59]; the NO production by the beans agglutinin can reduce the platelet aggregation, explaining the lower platelet activation compared with agglutinin from whole grain [60].

Many components from *Phaseolus* can help with the regulation of platelet aggregation as glycine by impeding the calcium influx [61], arginine by enhancing the nitric oxide activity in hypercholesterolemic patients [62], or anthocyanin by inhibiting the platelet-monocyte and platelet–endothelial interaction [63].

Derivatives of alpha-linoleic acid can inhibit platelet aggregation and inflammation, which has been linked to the prevention of CVD, hypertension, type 2 diabetes, chronic obstructive pulmonary disease, among others [19]. Especially, the role of omega3 and omega6 has been discussed many times for his role in platelet aggregation; many papers report the inhibitory effect of omega3 in ADP-dependent platelet aggregation [64][65], with a noticeable effect in healthy patients, unlike CVD patients who had a low increase in lag time [66]. Meanwhile, high omega 6 levels have been related to pro-inflammatory and pro-aggregatory phenotypes [67], by increasing the susceptibility of LDL to oxidate and therefore increasing the TXA2 production [68].

3.2. Effect on the Endothelium

The ingestion of inadequately cooked beans can result in severe glycemic index tract distress; the proposed mechanism of damage prevents the repair of the epithelial cell surface disruptions, resulting in necrotic cell death. The lectins are known to inhibit the exocytosis event required to repair the plasma membrane, and that is the mechanism used to maintain and accumulate the damage in the GI tract [69].

As we discussed, the common bean is cultivated worldwide and used as a nutraceutical food, when cooking properly, but is not the only process used to gain nutritional value from these pulses. The common bean hydrolysate had reported many effects from angiotensin-converting enzyme inhibitor to antioxidant, antimicrobial, and even tumor cell inhibitor. The bioactive potential of peptides present in the indigestible fraction of common beans that protect cells from oxidative stress and inhibit the angiotensin-I converting enzyme by interacting with its catalytic cavity independently of its antioxidant capacity was demonstrated [70].

Gomes et al. explained the hydrolysate capacity to modulate lipid metabolism and prevent endothelial dysfunction in BALB/c mice; they also showed hypocholesterolemic activity helping to reduce inflammation, oxidative stress, and endothelial dysfunction [71]. *Phaseolus vulgaris* L. agglutinin (PHA) evidenced specific cytoplasmic staining of macrophages in rabbit vessels, monkeys, and human tissues (atherosclerotic arteries obtained in surgery). When analyzing the morphometric comparisons between PHA staining of the lesion and acid lipase as a macrophage marker, similar results were obtained. In this context, they concluded that PHA is an excellent experimental marker to differentiate and quantify macrophages in fixed and human atherosclerotic lesions [72]. The use of hydrolysates of *Phaseolus vulgaris* shows an interesting effect in mice, from the modulation of the lipid profile to the increase in e-NOS expression [71]; this effect can be explained by the effect of the compounds found in the bean, upon endothelial cells. This is the case of n-3 PUFAs such as omega3 that, in trials, have shown prevention of endothelial dysfunction [73], or of amino acids such as lysine, leucine, serine and glutamine that work as modulators of NO production [74].

3.3. Effect on Inflammation

Some studies have focused on evaluating the effect of different plants with beneficial effects on pro-inflammatory mechanisms, mainly to reduce cardiovascular risk factors [75]. Macrophages are the main source of pro-inflammatory cytokines and can be used as markers of chronic inflammation, tumor necrosis factor α (TNF-α), interleukins (IL), and prostaglandins E-2 (PGE-2), among others. TNF-α plays a fundamental role in the expansion of the inflammatory process since it induces the production of IL-1β, among other pro-inflammatory cytokines [76], and increases PGE-2 [77][78].

Peroxisome Proliferator-Activated Receptors (PPARs) are transcription factors that belong to the superfamily of ligand-activated nuclear receptors, which mainly regulate lipid metabolism [79]. PPAR-α ligands are known to have anti-inflammatory effects in various cells through apoptosis in cytokine-activated macrophages, inhibiting NFκB signaling [79][80]. It has been described that the enzymatic hydrolysis of beans produces protein hydrolysates with anti-inflammatory activity [81] that could counteract the chronic inflammatory process initiated by human macrophages [78]. Research highlights the effectiveness of total digested proteins and peptides from bean seeds against adipogenic complications and inflammation [82]. Hydrolysate protein from this legume has been shown to decrease inflammation in adult male mice fed an atherogenic diet for nine weeks [71].

Phaseolin is the main globulin reserve in bean seeds [83]. This protein is a potential therapeutic candidate for the management of inflammation. Phaseolin inhibits nitric oxide production; inducible nitric oxide synthase expression also suppresses pro-inflammatory mediators such as cyclooxygenase 2 (COX-2), interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α), among others [84].

Oseguera et al. evaluated the antioxidant capacity of protein hydrolysates (rich in bioactive peptides derived from phaseolin) from the Negro 8025 and Pinto Durango varieties of *Phaseolus vulgaris* L. and determined their effect on the markers of inflammation in RAW 264.7 macrophages induced by lipopolysaccharides. Durango Pinto bean alcalase hydrolysates at 120 min inhibited inflammation (inhibition of cyclooxygenase (COX)-2 expression, prostaglandin E_2 production, inducible nitric oxide synthase (NOS) expression, and NO production) to a greater extent than black beans. Additionally, the hydrolysates inhibited the transactivation of NF-κB and the nuclear translocation of the p65 subunit of NF-κB [81].

Kim et al., 2016, studied the effects of adzuki beans on lipid accumulation and inflammation mediated by oxidative stress in male C57BL mice induced by a diet high in cholesterol and fat for 6 weeks. The results suggested that adzuki beans decrease lipid accumulation and inflammation induced by oxidative stress, by a mechanism of suppression of hepatic messenger RNA expression of lipogenic and inflammatory mediators. This effect could be associated with the rich anthocyanin, catechin, and saponin content of adzuki beans [85].

The effect of whole wheat flour and bean protein hydrolysate from the common bean variety Carioca on inflammation and oxidative stress was studied in BALB mice fed a diet high in fat and cholesterol. Animals fed whole bean meals showed less weight gain, higher levels of alanine aminotransferase, and low-density lipoprotein cholesterol than animals fed bean protein hydrolysate. The expression of PPAR-α was lower in the groups fed with bean protein hydrolysate and bean flour. These results could be associated with the increase in inflammation generated in diet-induced obesity since a short period was sufficient to decrease the inflammatory marker (PPAR). The positive effect on inflammation is attributable to phenolic compounds such as catechin and kaempferol present in bean flour, while in the protein hydrolysate; it is attributed to biologically active peptides and proteins such as phytohemagglutinin, alpha and beta phaseolin, alpha-amylase 1 inhibitor, and alpha-amylase 2 inhibitors [80][86].

Another study refers to how postharvest storage time influences the inflammation of Carioca, Madreperola, and Pontal beans, stored (0, 3, and 6 months), cooked, and subjected to simulated gastrointestinal digestion with pepsin–pancreatin. The study was conducted in human THP-1 macrophage-like cells. The commercial storage time did not affect the protein concentration, the degree of hydrolysis, the hydropathic, or the antioxidant capacity. All hydrolysates reduced TNF-α by about 30%. The Madreperola hydrolysates decreased IL-1β and PGE-2. Carioca beans inhibited inflammation due to their content of bioactive peptides and phenolic compounds, and it was shown that the commercial storage time did not affect the physicochemical or biological properties [78].

Studies have shown that the antioxidant and anti-inflammatory activities of bean extracts are associated with polyphenols present capable of inhibiting COX and lipoxygenase (LOX). Acetone extract made from black bean peel exhibited strong inhibitory effects of COX-1 (IC_{50} = 1.2 μg/mL) and COX-2 (IC_{50} = 38 μg/mL), while the aqueous extracts were stronger inhibitors of lipoxygenase, 15-LOX, versus the acetone extracts. The COX and LOX inhibitory activities of aqueous extracts such as acetone suggest that the use of bean shells in food may protect against some diseases associated with chronic inflammation [87]. People who consume beans and whole grains have been found to have a longer life expectancy and lower burden of chronic diseases, including obesity, CVD, diabetes, and cancer [88], which are characterized by having a strong chronic inflammatory component [89].

3.4. Effect on Metabolic Syndrome

Metabolic syndrome (METS) is a simultaneous group of metabolic disorders that includes central obesity (abdomen), insulin resistance, hypertension, glucose intolerance, and dyslipidemia [90], which increases the risk of CVD. It is estimated that it affects almost 35% of the US adult population, and its prevalence increases with age [91].

A healthy lifestyle, improving eating habits, and physical activity, are the therapeutic recommendations for the treatment and management of METS, but a gold standard dietary pattern for its management has not yet been proposed [92]. In this sense, many researchers have pointed out that a diet high in unsaturated fats, (olive oil), together with the consumption of legumes, cereals (whole grains), fruits, vegetables, nuts, fish, and low-fat dairy products, can prevent and delay the development of METS and prevent CVD [93].

One of the main causes of the development of this chronic syndrome is an imbalance between caloric consumption and expenditure. METS is associated with excessive activity of glucose metabolism enzymes and inflammatory processes [94]. Thus, a diet with low glycemic index products, such as *Phaseolus vulgaris* L., slows down the absorption of carbohydrates due to the inhibition of alpha-amylase and glucosidase enzymes, been proven in clinical trials [95].

Products that slow the absorption of carbohydrates by inhibiting the enzymes responsible for their digestion have been described as a powerful alternative to achieving a low-glycemic diet. These products include alpha-amylase and glucosidase inhibitors, which can reduce the risk of diabetes and heart disease and its complications. The common white bean (*Phaseolus vulgaris* L.) inhibits alpha-amylase by the action of the alpha-amylase inhibitor protein (αAI), which has been characterized and demonstrated in various clinical studies, demonstrating the ability of beans to cause weight loss (doses between 500 to 3000 mg per day). Conversely, the ability of this legume to reduce the postprandial peak in blood glucose levels depending on the dose has also been pointed out [95][96]. Common beans have three isoforms of alpha-amylase inhibitors (alpha-A1, alpha-A12, alpha-AIL). The alpha-AI isoform has anti-amylase activity in humans. This enzyme is only found in the embryonic axes and cotyledons of the plant seed. The alpha-amylase inhibitor prevents starch assimilation by completely blocking access to the active site of the enzyme. Some factors that affect the activity of the alpha-AI isoform inhibitor are pH, temperature, incubation time, and the presence of particular ions. Several authors have pointed out that the common bean reduces the rate of carbohydrate absorption, thus reducing the glycemic index of foods, as well as weight loss when consumed at the same time with carbohydrate-containing meals [95].

The consumption of legumes such as *Phaseolus vulgaris* L. provides bioactive molecules with an effect on obesity and metabolic syndrome, mainly due to a decrease in weight and triglyceride levels, although more quality trials must be performed to establish clinical efficacy [97]. In this sense, overweight individuals who received *Phaseolus vulgaris* L. extract had a significantly greater reduction in body weight index, fat mass, adipose tissue thickness, and anthropometric measurements of waist, hip, and thigh compared to the placebo group. The authors point out that this effect is based on the activity of αAI described in the extracts of *Phaseolus vulgaris* [98]; furthermore, the daily consumption of baked beans (*Phaseolus vulgaris* L.) for 14 days as part of a regular diet significantly decreased the mean total plasma cholesterol level of the volunteers: from 5.1 to 4.5 mmol/L ($p < 0.02$) [99]. This is correlated with the effect of dry beans, where it was identified that they reduce serum lipid concentrations in healthy and hyperlipidemic subjects, specifically serum cholesterol and triglyceride concentrations by 10.4% ($p < 0.001$) and 10.8% ($p < 0.025$), respectively, along with reducing body weight, despite constant energy intake, contributing to the management of hyperlipidemia present in METS due to its high content of soluble fiber, which alters the absorption of lipids in the intestine, affecting the synthesis of cholesterol to hepatic level [100].

In a clinical trial with 12 adults diagnosed with METS who ate one of three meals: black beans (BB), combined fiber (FM), and combined antioxidant capacity (AM), it was found that in the group that consumed black beans, postprandial insulinemia was lower after the meal compared to the other groups ($p < 0.0001$), and there was an improvement in plasma antioxidant capacity ($p = 0.002$), which could be explained by the fiber content of beans [101]. Similar effects were seen in healthy individuals, where consumption of *Phaseolus vulgaris* L. extract reduced postprandial glucose, insulin, and increased satiety [102]. Finally, 12 volunteers with METS were given in three different meals: no added fiber (control (NF), extrinsic or added fiber (AF), or whole black beans as a source of intrinsic fiber (BN). The BN meal produced a significant reduction in comparison with controls ($p < 0.0001$), showing beneficial effects in patients with METS [103]. In the context of animal models, in METS-induced male C57BL/6 mice, *Phaseolus vulgaris* L. extract reduced body weight and effectively lowered blood glucose, triglycerides, and cholesterol. At the same time, histological analysis of the aorta showed protection against the development of fatty streaks in the muscle layers. The authors conclude that the mechanism of action is due to the presence of αAI and alpha-glucosidase inhibitors [104]. In another investigation, treatment with a combination of *Phaseolus vulgaris* L. and *Cynara scolymus* extracts reduced food intake and blood glucose in rats [105].

Proteins are abundant components in beans. The positive effect on blood pressure reduction of bean protein hydrolysates has been reported in hypertensive rats, which is attributed to the ability of peptides to inhibit angiotensin-converting enzyme (ACE) [71][106]. Glutelin hydrolysates show a potent ACE inhibitory activity of around 80.24%. The results show that glutelin could be an effective hypertensive in ACE [107]. Conversely, the administration of a black bean protein hydrolysate at a concentration of 200 mg/kg showed a hypoglycemic effect in rats [71][108]. Studies have highlighted that starch-enriched diets lower cholesterol levels, improving dyslipidemia and body composition. A double-blind, placebo-controlled crossover intervention showed that individuals who consumed a diet rich in starch for 12 weeks show favorable results for the promotion of these diets in public cardiometabolic health [109]. Another study examined the effect of starch on hypolipidemic actions, blood glucose, insulin levels, and humoral immune responses in healthy, overweight subjects who were fed 24 g/day of resistant cornstarch or regular cornstarch for 21 days. Reducing effects of total serum cholesterol and serum LDL cholesterol were evidenced. These results suggest that starch supplementation improves blood lipid profile and controls blood glucose levels in healthy overweight subjects [110].

Many studies suggest the effect of linoleic acid on obesity, cancer, atherosclerosis, among other health benefits. Linoleic acid has been shown to promote fat loss in rodent models [111]. Initial studies in male and female mice showed that a mixed diet supplemented with conjugated linoleic acid promotes fat loss by 60% for 30 days; this effect was attributed to increased lipolysis and fat oxidation [111][112]. Recently, it has been recognized that supplementation with this acid reduces fat stores, and dramatically decreases circulating adiponectin levels in mice [111][113].

Evidence suggests that the consumption of derivatives of *Phaseolus vulgaris* L. reduces food intake, body weight, lipid deposition, and blood glucose in rats due to the inhibition of α-amylase, reducing carbohydrate metabolism [114]. Together, these data in animal models and clinical trials demonstrate the potential effect of *Phaseolus vulgaris* L. to treat obesity and METS, consecutively decreasing the development of thrombotic events.

3.5. Effect of Beans on Atherosclerosis

Studies have shown that diet attenuates atherosclerosis, the mechanisms of which are related to less atherogenic dyslipidemia, relief of intestinal dysbiosis, and suppressed inflammation [115]. The atherosclerotic process is established from the increase of pro-atherogenic and pro-inflammatory mediators that favor plaque formation and progressive stenosis [116][117]. The initial step of atherosclerosis is associated whit high levels of low-density lipoproteins (LDL), oxidation of LDL, and recruitment of monocytes [117][118]. The accumulation of cholesterol-laden macrophage foam cells is a key feature of atherosclerotic lesions. Cholesterol can enter macrophages through various pathways and induce the transformation of macrophages into foam cells [119].

Studies have shown that beans can improve lipid profiles associated with the development of atherosclerotic lesions and the prevalence of CVD. Consuming beans lower cholesterol without affecting serum triglycerides, VLDL cholesterol, or blood glucose [120]. Oxidized LDL (ox-LDL) and its interaction with the ox-LDL lectin receptor (LOX-1) determine the progression of atherosclerosis. Peptides from carioca beans have shown antiatherosclerotic properties comparable to simvastatin, through inhibition of LOX-1, MMP-9, and ICAM-1 and inhibition of 10 cytokines related to the atherosclerotic process (128). Research shows that chia, a variety of beans, is considered a good source of dietary fiber, protein, antioxidants, and bioactive lipids [121][122]. In recent years, chia seeds have gained great importance due to their high alpha-linolenic acid content (68%) and their relationship to human health and nutrition [123].

Various studies have indicated that this compound has cardioprotective properties by affecting specific biomarkers (lactate dehydrogenase; LDH) [124]. The background shows that conjugated linoleic acid has the potential to inhibit cholesterol-induced atherosclerosis in rabbits and hamsters, respectively [125]. Conjugated linoleic acid inhibits experimentally induced atherosclerosis in rabbits fed an atherogenic diet. A reduction in pre-established atheromatous lesions was evidenced [126]. Conjugated linoleic acid reduced early aortic atherosclerosis to a greater extent than linoleic acid in a hypercholesterolemic hamster population. These effects may be related to changes in the oxidative susceptibility of LDL in hypercholesterolemic hamsters [127].

The intake of dietary fiber has been associated with an inhibition of the development of atherosclerosis in animal models [128], while soluble fiber reduces serum cholesterol and LDL cholesterol concentrations [128][129]. In general, proteins of animal origin are more cholesterolemias and atherogenic than proteins of plant origin [130]. Research has highlighted that the oral administration of peptides synthesized from amino acids reduces atherosclerosis independently of plasma cholesterol in a group of mice, thus improving the capacity of high-density lipoproteins (HDL) in the study population [131]. Specific studies with different varieties of beans have shown that the consumption of this legume reduces 10% of the cholesterol levels of normal young men after ingestion of 450 g/d of canned baked beans compared to the control group [99]. A 10% reduction in serum cholesterol levels was also reported in hyperlipidemic men fed 120–162 g/d of pinto beans [100].

Celleno et al. showed that overweight subjects who consumed a dietary formula with *Phaseolus vulgaris* L. extract as the main ingredient, significantly decrease body fat due to the interference caused by this legume in the digestion of carbohydrates, thus contributing to the prevention of atherosclerosis by reducing fats in organs and tissues [98]. *Phaseolus vulgaris* L. provides micronutrients, particularly folic acid and magnesium, and its high content of fiber, sulfur amino acids, tannins, phytoestrogens, and non-essential amino acids have been linked to the prevention of atherosclerotic lesions. The prevention of atherosclerosis is a powerful tool in the prevention of cardiovascular events, as this silent pathology is responsible for about half of deaths from heart disease [19][132].

References

1. Irfan, M.; Kwon, T.-H.; Lee, D.-H.; Hong, S.-B.; Oh, J.-W.; Kim, S.-D.; Rhee, M.H. Antiplatelet and antithrombotic effects of Epimedium koreanum Nakai. Evid.-Based Complement. Altern. Med. 2021, 2021, 7071987.
2. Olas, B. Dietary supplements with antiplatelet activity: A solution for everyone? Adv. Nutr. 2018, 9, 51–57.
3. Jackson, S.L.; Yang, E.C.; Zhang, Z. Income disparities and cardiovascular risk factors among adolescents. Pediatrics 2018, 142, e20181089.
4. Mensah, G.A.; Roth, G.A.; Fuster, V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. J. Am. Coll. Cardiol. 2019, 74, 2529–2532.
5. Rosengren, A.; Hawken, S.; Ôunpuu, S.; Sliwa, K.; Zubaid, M.; Almahmeed, W.A.; Ngu Blackett, K.; Sitthi-Amorn, C.; Sato, H.; Yusuf, S.; et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11,119 cases and 13,648 controls from 52 countries (the INTERHEART study): Case-control study. Lancet 2004, 364, 953–962.
6. Cuadrado-Godia, E.; Jamthikar, A.D.; Gupta, D.; Khanna, N.N.; Araki, T.; Maniruzzaman, M.; Saba, L.; Nicolaides, A.; Sharma, A.; Omerzu, T.; et al. Ranking of stroke and cardiovascular risk factors for an optimal risk calculator design: Logistic regression approach. Comput. Biol. Med. 2019, 108, 182–195.
7. Kalantar-Zadeh, K.; Block, G.; Humphreys, M.H.; Kopple, J.D. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int. 2003, 63, 793–808.
8. Niccoli, T.; Partridge, L. Ageing as a risk factor for disease. Curr. Biol. 2012, 22, R741–R752.
9. Strait, J.B.; Lakatta, E.G. Aging-associated cardiovascular changes and their relationship to heart failure. Heart Fail. Clin. 2012, 8, 143–164.
10. Zhang, S.; Liu, Y.; Wang, X.; Yang, L.; Li, H.; Wang, Y.; Liu, M.; Zhao, X.; Xie, Y.; Yang, Y.; et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J. Hematol. Oncol. 2020, 13, 120.
11. Huang, J.; Li, X.; Shi, X.; Zhu, M.; Wang, J.; Huang, S.; Huang, X.; Wang, H.; Li, L.; Deng, H.; et al. Platelet integrin αIIbβ3: Signal transduction, regulation, and its therapeutic targeting. J. Hematol. Oncol. 2019, 12, 26.

12. Meshkini, A.; Tahmasbi, M. Antiplatelet aggregation activity of walnut hull extract via suppression of reactive oxygen species generation and caspase activation. J. Acupunct. Meridian Stud. 2017, 10, 193–203.
13. Tsoupras, A.; Lordan, R.; Zabetakis, I. Thrombosis and COVID-19: The potential role of nutrition. Front. Nutr. 2020, 7, 177.
14. Tsoupras, A.; Lordan, R.; Zabetakis, I. Inflammation, not cholesterol, is a cause of chronic disease. Nutrients 2018, 10, 604.
15. Yu, E.; Malik, V.S.; Hu, F.B. Cardiovascular disease prevention by diet modification: JACC health promotion series. J. Am. Coll. Cardiol. 2018, 72, 914–926.
16. Calder, P.C.; Carr, A.C.; Gombart, A.F.; Eggersdorfer, M. optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients 2020, 12, 1181.
17. Bartimoccia, S.; Nocella, C.; Pastori, D.; Pignatelli, P.; Carnevale, R. Platelet oxidative stress and antioxidant nutrients. J. Vasc. Med. Surg. 2014, 2, 1000164.
18. Violi, F.; Pignatelli, P. Platelet oxidative stress and thrombosis. Thromb. Res. 2012, 129, 378–381.
19. Câmara, C.R.S.; Urrea, C.A.; Schlegel, V. Pinto beans (Phaseolus vulgaris L.) as a functional food: Implications on human health. Agriculture 2013, 3, 90–111.
20. Bellucci, E.; Bitocchi, E.; Rau, D.; Rodriguez, M.; Biagetti, E.; Giardini, A.; Attene, G.; Nanni, L.; Papa, R. Genomics of origin, domestication and evolution of Phaseolus vulgaris. Genom. Plant Genet. Resour. 2014, 483–507.
21. Yanez, E.; Zacarias, I.; Aguayo, M.; Vasquez, M.; Guzman, E. Nutritive value evaluated on rats of new cultivars of common beans (Phaseolus vulgaris) released in Chile. Plant Foods Hum. Nutr. 1995, 47, 301–307.
22. de Almeida Costa, G.E.; da Silva Queiroz-Monici, K.; Reis, S.M.P.M.; de Oliveira, A.C. Chemical composition, dietary fibre and resistant starch contents of raw and cooked pea, common bean, chickpea and lentil legumes. Food Chem. 2006, 94, 327–330.
23. Lin, L.-Z.; Harnly, J.M.; Pastor-Corrales, M.S.; Luthria, D.L. The polyphenolic profiles of common bean (Phaseolus vulgaris L.). Food Chem. 2008, 107, 399–410.
24. Tharanathan, R.N.; Mahadevamma, S. Grain legumes—A boon to human nutrition. Trends Food Sci. Technol. 2003, 14, 507–518.
25. Shimelis, E.A.; Rakshit, S.K. Proximate composition and physico-chemical properties of improved dry bean (Phaseolus vulgaris L.) varieties grown in Ethiopia. LWT-Food Sci. Technol. 2005, 38, 331–338.

26. Hayat, I.; Ahmad, A.; Masud, T.; Ahmed, A.; Bashir, S. Nutritional and health perspectives of beans (Phaseolus vulgaris L.): An overview. Crit. Rev. Food Sci. Nutr. 2014, 54, 580–592.
27. Siddiq, M.; Ravi, R.; Harte, J.B.; Dolan, K.D. Physical and functional characteristics of selected dry bean (Phaseolus vulgaris L.) flours. LWT-Food Sci. Technol. 2010, 43, 232–237.
28. Landon, A.J. The “how” of the three sisters: The origins of agriculture in Mesoamerica and the human niche. Neb. Anthropol. 2008, 23, 110–124.
29. Celmeli, T.; Sari, H.; Canci, H.; Sari, D.; Adak, A.; Eker, T.; Toker, C. The nutritional content of common bean (Phaseolus vulgaris L.) landraces in comparison to modern varieties. Agronomy 2018, 8, 166.
30. Gepts, P. Phaseolus vulgaris (beans). Encycl. Genet. 2001, 1444–1445.
31. Singh, S.P. Broadening the genetic base of common bean cultivars: A review. Crop Sci. 2001, 41, 1659–1675.
32. Bitocchi, E.; Rau, D.; Bellucci, E.; Rodriguez, M.; Murgia, M.L.; Gioia, T.; Santo, D.; Nanni, L.; Attene, G.; Papa, R. Beans (Phaseolus ssp.) as a model for understanding crop evolution. Front. Plant Sci. 2017, 8, 722.
33. Acosta-Gallegos, J.A.; Kelly, J.D.; Gepts, P. Prebreeding in common bean and use of genetic diversity from wild germplasm. Crop Sci. 2007, 47, S-44–S-59.
34. Marquezi, M.; Gervin, V.M.; Watanabe, L.B.; Moresco, R.; Amante, E.R. Chemical and functional properties of different common Brazilian bean (Phaseolus vulgaris L.) cultivars. Braz. J. Food Technol. 2017, 20, e2016006.
35. Leterme, P.; Muũoz, L.C. Factors influencing pulse consumption in Latin America. Br. J. Nutr. 2002, 88, 251–254.
36. Luthria, D.L.; Pastor-Corrales, M.A. Phenolic acids content of fifteen dry edible bean (Phaseolus vulgaris L.) varieties. J. Food Compos. Anal. 2006, 19, 205–211.
37. Akibode, C.S.; Maredia, M.K. Global and Regional Trends in Production, Trade and Consumption of Food Legume Crops. 2012. Available online: https://ageconsearch.umn.edu/record/136293 (accessed on 15 October 2012).
38. Paredes, M.; Becerra, V.; Tay, J. Inorganic nutritional composition of common bean (Phaseolus vulgaris L.) genotypes race Chile. Chil. J. Agric. Res. 2009, 69, 486–495.
39. Shellie-Dessert, K.C.; Bliss, F.A. Genetic improvement of food quality factors. In Common Beans: Research for Crop Improvement; Schoonhoven, A., vanVoysest, O., Eds.; CAB International: Wallingford, UK, 1991; pp. 649–677.

40. Choung, M.-G.; Choi, B.-R.; An, Y.-N.; Chu, Y.-H.; Cho, Y.-S. Anthocyanin profile of Korean cultivated kidney bean (Phaseolus vulgaris L.). J. Agric. Food Chem. 2003, 51, 7040–7043.
41. Aparicio-Fernández, X.; García-Gasca, T.; Yousef, G.G.; Lila, M.A.; González de Mejia, E.; Loarca-Pina, G. Chemopreventive activity of polyphenolics from black Jamapa bean (Phaseolus vulgaris L.) on HeLa and HaCaT cells. J. Agric. Food Chem. 2006, 54, 2116–2122.
42. Hosfield, G.L.; Varner, G.V.; Uebersax, M.A.; Kelly, J.D. Registration of 'Merlot' small red bean. Crop Sci. 2004, 44, 351–353.
43. Amir, Y.; Haenni, A.L.; Youyou, A. Differences in the biochemical composition of dry legumes cultivated in north Algeria. Electron J. Environ. Agric Food Chem. 2006, 5, 1411–1418.
44. Baginsky, C.; Ramos, L. Situación de las legumbres en Chile: Una mirada agronómica. Rev. Chil. Nutr. 2018, 45, 21–31.
45. Broughton, W.J.; Hernandez, G.; Blair, M.; Beebe, S.; Gepts, P.; Vanderleyden, J. Beans (Phaseolus spp.)—Model food legumes. Plant Soil 2003, 252, 55–128.
46. Baginsky, C.; Brito, B.; Scherson, R.; Pertuzé, R.; Seguel, O.; Cañete, A.; Araneda, C.; Johnson, W. Genetic diversity of Rhizobium from nodulating beans grown in a variety of Mediterranean climate soils of Chile. Arch. Microbiol. 2015, 197, 419–429.
47. Olanipekun, O.T.; Omenna, E.C.; Olapade, O.A.; Suleiman, P.; Omodara, O.G. Effect of boiling and roasting on the nutrient composition of kidney beans seed flour. Sky J. Food Sci. 2015, 4, 24–29.
48. Singh, S.P.; Gepts, P.; Debouck, D.G. Races of common bean (Phaseolus vulgaris, Fabaceae). Econ. Bot. 1991, 45, 379–396.
49. Bascur, G.B.; Tay, J.U. Collection, characterization and use of genetic variation in Chilean bean germplasm (Phaseolus vulgaris L.) 1. Agric. Técnica 2005, 65, 135–146.
50. Trucchi, E.; Benazzo, A.; Lari, M.; Iob, A.; Vai, S.; Nanni, L.; Bellucci, E.; Bitocchi, E.; Raffini, F.; Xu, C.; et al. Ancient genomes reveal early Andean farmers selected common beans while preserving diversity. Nat. Plants 2021, 7, 123–128.
51. Olas, B. The multifunctionality of berries toward blood platelets and the role of berry phenolics in cardiovascular disorders. Platelets 2017, 28, 540–549.
52. Fuentes, E.; Palomo, I. Antiplatelet effects of natural bioactive compounds by multiple targets: Food and drug interactions. J. Funct. Foods 2014, 6, 73–81.
53. Rodríguez-Azúa, R.; Quinteros, E.F.; Olate-Briones, A.; Moore-Carrasco, R. Phaseolus vulgaris exerts an inhibitory effect on platelet aggregation through AKT dependent way. Prev. Nutr. Food Sci. 2018, 23, 102.

54. Vaiyapuri, S.; Roweth, H.; Ali, M.S.; Unsworth, A.J.; Stainer, A.R.; Flora, G.D.; Crescente, M.; Jones, C.I.; Moraes, L.A.; Gibbins, J.M. Pharmacological actions of nobiletin in the modulation of platelet function. Br. J. Pharmacol. 2015, 172, 4133–4145.
55. Ganguly, P.; Gould, N.L.; Sidhu, P. Interaction of lectins with human platelets: Effects of platelet stimulation by thrombin and ristocetin. Biochim. Biophys. Acta (BBA)-Gen. Subj. 1979, 586, 574–583.
56. Signorello, M.G.; Ravera, S.; Leoncini, G. Lectin-induced oxidative stress in human platelets. Redox Biol. 2020, 32, 101456.
57. Kinlough-Rathbone, R.L.; Mustard, J.F.; Packham, M.A.; Perry, D.W.; Reimers, H.-J.; Cazenave, J.-P. Properties of washed human platelets. Thromb. Haemost. 1977, 37, 291–308.
58. Cazenave, J.P.; Guccione, M.A.; Packham, M.A.; Mustard, J.F. Effects of cephalothin and penicillin G on platelet function in vitro. Br. J. Haematol. 1977, 35, 135–152.
59. Signorello, M.G.; Leoncini, G. The Ca2+/calmodulin kinase/AMP-activated protein kinase pathway regulates the lectin Phaseolus vulgaris agglutinin induced NO production in human platelets. Integr. Mol. Med. 2019, 6, 1–9.
60. Wang, G.-R.; Zhu, Y.; Halushka, P.V.; Lincoln, T.M.; Mendelsohn, M.E. Mechanism of platelet inhibition by nitric oxide: In vivo phosphorylation of thromboxane receptor by cyclic GMP-dependent protein kinase. Proc. Natl. Acad. Sci. USA 1998, 95, 4888–4893.
61. Schemmer, P.; Zhong, Z.; Galli, U.; Wheeler, M.D.; Xiangli, L.; Bradford, B.U.; Conzelmann, L.O.; Forman, D.; Boyer, J.; Thurman, R.G. Glycine reduces platelet aggregation. Amino Acids 2013, 44, 925–931.
62. Wolf, A.; Zalpour, C.; Theilmeier, G.; Wang, B.-Y.; Ma, A.; Anderson, B.; Tsao, P.S.; Cooke, J.P. Dietary L-arginine supplementation normalizes platelet aggregation in hypercholesterolemic humans. J. Am. Coll. Cardiol. 1997, 29, 479–485.
63. Thompson, K.; Hosking, H.; Pederick, W.; Singh, I.; Santhakumar, A.B. The effect of anthocyanin supplementation in modulating platelet function in sedentary population: A randomised, double-blind, placebo-controlled, cross-over trial. Br. J. Nutr. 2017, 118, 368–374.
64. Adili, R.; Hawley, M.; Holinstat, M. Regulation of platelet function and thrombosis by omega-3 and omega-6 polyunsaturated fatty acids. Prostaglandins Other Lipid Mediat. 2018, 139, 10–18.
65. Dratewka-Kos, E.; Tinker, D.O.; Kindl, B. Unsaturated fatty acids inhibit ADP-arachidonate-induced platelet aggregation without affecting thromboxane synthesis. Biochem. Cell Biol. 1986, 64, 906–913.
66. McEwen, B.J.; Morel-Kopp, M.-C.; Chen, W.; Tofler, G.H.; Ward, C.M. Effects of omega-3 polyunsaturated fatty acids on platelet function in healthy subjects and subjects with

cardiovascular disease. Semin. Thromb. Hemost. 2013, 39, 25–32.

67. Hodgson, J.M.; Wahlqvist, M.L.; Boxall, J.A.; Balazs, N.D. Can linoleic acid contribute to coronary artery disease? Am. J. Clin. Nutr. 1993, 58, 228–234.
68. Dinicolantonio, J.; Okeefe, J. Importance of maintaining a low omega-6/omega-3 ratio for reducing platelet aggregation, coagulation and thrombosis. Open Heart 2019, 6, e001011.
69. Miyake, K.; Tanaka, T.; McNeil, P.L. Lectin-based food poisoning: A new mechanism of protein toxicity. PLoS ONE 2007, 2, e687.
70. Luna-Vital, D.A.; De Mejía, E.G.; Mendoza, S.; Loarca-Piña, G. Peptides present in the non-digestible fraction of common beans (Phaseolus vulgaris L.) inhibit the angiotensin-I converting enzyme by interacting with its catalytic cavity independent of their antioxidant capacity. Food Funct. 2015, 6, 1470–1479.
71. Gomes, M.J.; Lima, S.L.; Alves, N.E.G.; Assis, A.; Moreira, M.E.; Toledo, R.C.; Rosa, C.O.; Teixeira, O.R.; Bassinello, P.Z.; De Mejía, E.G.; et al. Common bean protein hydrolysate modulates lipid metabolism and prevents endothelial dysfunction in BALB/c mice fed an atherogenic diet. Nutr. Metab. Cardiovasc. Dis. 2020, 30, 141–150.
72. Davis, H.R.; Glagov, S. Lectin binding to distinguish cell types in fixed atherosclerotic arteries. Atherosclerosis 1986, 61, 193–203.
73. Zehr, K.R.; Walker, M.K. Omega-3 polyunsaturated fatty acids improve endothelial function in humans at risk for atherosclerosis: A review. Prostaglandins Other Lipid Mediat. 2018, 134, 131–140.
74. Kakoki, M.; Kim, H.-S.; Edgell, C.-J.S.; Maeda, N.; Smithies, O.; Mattson, D.L. Amino acids as modulators of endothelium-derived nitric oxide. Am. J. Physiol.-Ren. Physiol. 2006, 291, F297–F304.
75. Gamboa-Gomez, C.I.; Rocha-Guzman, N.E.; Gallegos-Infante, J.A.; Moreno-Jimenez, M.R.; Vazquez-Cabral, B.D.; Gonzalez-Laredo, R.F. Plants with potential use on obesity and its complications. EXCLI J. 2015, 14, 809–831.
76. Lefkowitz, D.L.; Lefkowitz, S.S. Macrophage–neutrophil interaction: A paradigm for chronic inflammation revisited. Immunol. Cell Biol. 2001, 79, 502–506.
77. Williams, C.S.; Mann, M.; DuBois, R.N. The role of cyclooxygenases in inflammation, cancer, and development. Oncogene 1999, 18, 7908–7916.
78. Alves, N.E.G.; de Mejía, E.G.; Vasconcelos, C.M.; Bassinello, P.Z.; Martino, H.S.D. Postharvest storage of Carioca bean (Phaseolus vulgaris L.) did not impair inhibition of inflammation in lipopolysaccharide-induced human THP-1 macrophage-like cells. J. Funct. Foods 2016, 23, 154–166.

79. Monsalve, F.A.; Pyarasani, R.D.; Delgado-Lopez, F.; Moore-Carrasco, R. Peroxisome proliferator-activated receptor targets for the treatment of metabolic diseases. Mediat. Inflamm. 2013, 2013, 549627.
80. de Lima, S.L.S.; Gomes, M.J.C.; da Silva, B.P.; Alves, N.E.G.; Toledo, R.C.L.; Theodoro, J.M.V.; Moreira, M.E.C.; Bento, J.A.C.; Bassinello, P.Z.; da Matta, S.L.P.; et al. Whole flour and protein hydrolysate from common beans reduce the inflammation in BALB/c mice fed with high fat high cholesterol diet. Food Res. Int. 2019, 122, 330–339.
81. Oseguera-Toledo, M.E.; De Mejia, E.G.; Dia, V.P.; Amaya-Llano, S.L. Common bean (Phaseolus vulgaris L.) hydrolysates inhibit inflammation in LPS-induced macrophages through suppression of NF-κB pathways. Food Chem. 2011, 127, 1175–1185.
82. Grancieri, M.; Martino, H.S.D.; de Mejia, E.G. Protein Digests and pure peptides from chia seed prevented adipogenesis and inflammation by inhibiting PPARγ and NF-κB pathways in 3T3L-1 adipocytes. Nutrients 2021, 13, 176.
83. Derbyshire, E.; Wright, D.J.; Boulter, D. Legumin and vicilin, storage proteins of legume seeds. Phytochemistry 1976, 15, 3–24.
84. Hwang, S.-J.; Song, Y.-S.; Lee, H.-J. Phaseolin attenuates lipopolysaccharide-induced inflammation in RAW 264.7 cells and zebrafish. Biomedicines 2021, 9, 420.
85. Kim, S.; Hong, J.; Jeon, R.; Kim, H.-S. Adzuki bean ameliorates hepatic lipogenesis and proinflammatory mediator expression in mice fed a high-cholesterol and high-fat diet to induce nonalcoholic fatty liver disease. Nutr. Res. 2016, 36, 90–100.
86. Rodríguez, E.; Ribot, J.; Rodríguez, A.M.; Palou, A. PPAR-γ2 expression in response to cafeteria diet: Gender- and depot-specific effects. Obes. Res. 2004, 12, 1455–1463.
87. Oomah, B.D.; Corbé, A.; Balasubramanian, P. Antioxidant and anti-inflammatory activities of bean (Phaseolus vulgaris L.) hulls. J. Agric. Food Chem. 2010, 58, 8225–8230.
88. Borresen, E.C.; Brown, D.G.; Harbison, G.; Taylor, L.; Fairbanks, A.; O'Malia, J.; Bazan, M.; Rao, S.; Bailey, S.M.; Wdowik, M.; et al. A randomized controlled trial to increase navy bean or rice bran consumption in colorectal cancer survivors. Nutr. Cancer 2016, 68, 1269–1280.
89. Kunnumakkara, A.B.; Sailo, B.L.; Banik, K.; Harsha, C.; Prasad, S.; Gupta, S.C.; Bharti, A.C.; Aggarwal, B.B. Chronic diseases, inflammation, and spices: How are they linked? J. Transl. Med. 2018, 16, 14.
90. Shi, Y.; Zou, Y.; Shen, Z.; Xiong, Y.; Zhang, W.; Liu, C.; Chen, S. Trace Elements, PPARs, and Metabolic Syndrome. Int. J. Mol. Sci. 2020, 21, 2612.
91. Katsimardou, A.; Imprialos, K.; Stavropoulos, K.; Sachinidis, A.; Doumas, M.; Athyros, V. Hypertension in metabolic syndrome: Novel Insights. Curr. Hypertens. Rev. 2020, 16, 12–18.

92. Castro-Barquero, S.; Ruiz-Leon, A.M.; Sierra-Perez, M.; Estruch, R.; Casas, R. Dietary strategies for metabolic syndrome: A comprehensive review. Nutrients 2020, 12, 2983.
93. Perez-Martinez, P.; Mikhailidis, D.P.; Athyros, V.G.; Bullo, M.; Couture, P.; Covas, M.I.; de Koning, L.; Delgado-Lista, J.; Díaz-López, A.; Drevon, C.A.; et al. Lifestyle recommendations for the prevention and management of metabolic syndrome: An international panel recommendation. Nutr. Rev. 2017, 75, 307–326.
94. Jakubczyk, A.; Karas, M.; Zlotek, U.; Szymanowska, U. Identification of potential inhibitory peptides of enzymes involved in the metabolic syndrome obtained by simulated gastrointestinal digestion of fermented bean (Phaseolus vulgaris L.) seeds. Food Res. Int. 2017, 100, 489–496.
95. Barrett, M.L.; Udani, J.K. A proprietary alpha-amylase inhibitor from white bean (Phaseolus vulgaris): A review of clinical studies on weight loss and glycemic control. Nutr. J. 2011, 10, 24.
96. Sales, P.M.; Souza, P.M.; Simeoni, L.A.; Magalhães, P.O.; Silveira, D. α-Amylase inhibitors: A review of raw material and isolated compounds from plant source. J. Pharm. Pharm. Sci. 2012, 15, 141–183.
97. Payab, M.; Hasani-Ranjbar, S.; Shahbal, N.; Qorbani, M.; Aletaha, A.; Haghi-Aminjan, H.; Soltani, A.; Khatami, F.; Nikfar, S.; Hassani, S.; et al. Effect of the herbal medicines in obesity and metabolic syndrome: A systematic review and meta-analysis of clinical trials. Phytother. Res. 2020, 34, 526–545.
98. Celleno, L.; Tolaini, M.V.; D’Amore, A.; Perricone, N.V.; Preuss, H.G. A dietary supplement containing standardized Phaseolus vulgaris extract influences body composition of overweight men and women. Int. J. Med. Sci. 2007, 4, 45–52.
99. Shutler, S.M.; Bircher, G.M.; Tredger, J.A.; Morgan, L.M.; Walker, A.F.; Low, A.G. The effect of daily baked bean (Phaseolus vulgaris) consumption on the plasma lipid levels of young, normo-cholesterolaemic men. Br. J. Nutr. 1989, 61, 257–265.
100. Anderson, J.W.; Gustafson, N.J.; Spencer, D.B.; Tietyen, J.; Bryant, C.A. Serum lipid response of hypercholesterolemic men to single and divided doses of canned beans. Am. J. Clin. Nutr. 1990, 51, 1013–1019.
101. Reverri, E.J.; Randolph, J.M.; Steinberg, F.M.; Kappagoda, C.T.; Edirisinghe, I.; Burton-Freeman, B.M. black beans, fiber, and antioxidant capacity pilot study: Examination of whole foods vs. functional components on postprandial metabolic, oxidative stress, and inflammation in adults with metabolic syndrome. Nutrients 2015, 7, 6139–6154.
102. Spadafranca, A.; Rinelli, S.; Riva, A.; Morazzoni, P.; Magni, P.; Bertoli, S.; Battezzati, A. Phaseolus vulgaris extract affects glycometabolic and appetite control in healthy human subjects. Br. J. Nutr. 2013, 109, 1789–1795.

103. Reverri, E.J.; Randolph, J.M.; Kappagoda, C.T.; Park, E.; Edirisinghe, I.; Burton-Freeman, B.M. Assessing beans as a source of intrinsic fiber on satiety in men and women with metabolic syndrome. Appetite 2017, 118, 75–81.
104. Micheli, L.; Lucarini, E.; Trallori, E.; Avagliano, C.; De Caro, C.; Russo, R.; Calignano, A.; Ghelardini, C.; Pacini, A.; Di Cesare Mannelli, L. Phaseolus vulgaris L. extract: Alpha-amylase inhibition against metabolic syndrome in mice. Nutrients 2019, 11, 1778.
105. Zaru, A.; Maccioni, P.; Riva, A.; Morazzoni, P.; Bombardelli, E.; Gessa, G.L.; Morazzoni, P.; Carai, M.A.M. Reducing effect of a combination of Phaseolus vulgaris and Cynara scolymus extracts on operant self-administration of a chocolate-flavoured beverage in rats. Phytother. Res. 2013, 27, 944–947.
106. Li, G.-H.; Shi, Y.-H.; Liu, H.; Le, G.-W. Antihypertensive effect of alcalase generated mung bean protein hydrolysates in spontaneously hypertensive rats. Eur. Food Res. Technol. 2006, 222, 733–736.
107. Zheng, Y.; Li, Y.; Zhang, Y.; Ruan, X.; Zhang, R. Purification, characterization, synthesis, in vitro ACE inhibition and in vivo antihypertensive activity of bioactive peptides derived from oil palm kernel glutelin-2 hydrolysates. J. Funct. Foods 2017, 28, 48–58.
108. Mojica, L.; de Mejia, E.G.; Granados-Silvestre, M.Á.; Menjivar, M. Evaluation of the hypoglycemic potential of a black bean hydrolyzed protein isolate and its pure peptides using in silico, in vitro and in vivo approaches. J. Funct. Foods 2017, 31, 274–286.
109. Nichenametla, S.N.; Weidauer, L.A.; Wey, H.E.; Beare, T.M.; Specker, B.L.; Dey, M. Resistant starch type 4-enriched diet lowered blood cholesterols and improved body composition in a double blind controlled cross-over intervention. Mol. Nutr. Food Res. 2014, 58, 1365–1369.
110. Park, O.J.; Ekang, N.; Chang, M.J.; Kim, W.K. Resistant starch supplementation influences blood lipid concentrations and glucose control in overweight subjects. J. Nutr. Sci. Vitaminol. 2004, 50, 93–99.
111. den Hartigh, L.J. Conjugated linoleic acid effects on cancer, obesity, and atherosclerosis: A review of pre-clinical and human trials with current perspectives. Nutrients 2019, 11, 370.
112. Park, Y.; Albright, K.J.; Liu, W.; Storkson, J.M.; Cook, M.E.; Pariza, M.W. Effect of conjugated linoleic acid on body composition in mice. Lipids 1997, 32, 853–858.
113. Miller, J.R.; Siripurkpong, P.; Hawes, J.; Majdalawieh, A.; Ro, H.-S.; McLeod, R.S. The trans-10, cis-12 isomer of conjugated linoleic acid decreases adiponectin assembly by PPARγ-dependent and PPARγ-independent mechanisms. J. Lipid Res. 2008, 49, 550–562.
114. Carai, M.A.; Fantini, N.; Loi, B.; Colombo, G.; Riva, A.; Morazzoni, P. Potential efficacy of preparations derived from Phaseolus vulgaris in the control of appetite, energy intake, and carbohydrate metabolism. Diabetes Metab. Syndr. Obes. Targets Ther. 2009, 2, 145–153.

115. Guo, W.; Kim, S.H.; Wu, D.; Li, L.; Ortega, E.F.; Thomas, M.; Meydani, S.N.; Meydani, M. Dietary fruit and vegetable supplementation suppresses diet-induced atherosclerosis in LDL receptor knockout mice. J. Nutr. 2021, 151, 902–910.
116. Khan, R.; Spagnoli, V.; Tardif, J.-C.; L'Allier, P.L. Novel anti-inflammatory therapies for the treatment of atherosclerosis. Atherosclerosis 2015, 240, 497–509.
117. Alves, N.E.G.; Vasconcelos, C.M.; Bassinello, P.Z.; de Mejia, E.G.; Martino, H.S.D. Digested protein isolate from fresh and stored Carioca beans reduced markers of atherosclerosis in oxidized LDL-induced THP-1 macrophages. J. Funct. Foods 2016, 24, 97–111.
118. Neele, A.E.; Van den Bossche, J.; Hoeksema, M.A.; De Winther, M.P.J. Epigenetic pathways in macrophages emerge as novel targets in atherosclerosis. Eur. J. Pharmacol. 2015, 763, 79–89.
119. Soltani, S.; Boozari, M.; Cicero, A.F.G.; Jamialahmadi, T.; Sahebkar, A. Effects of phytochemicals on macrophage cholesterol efflux capacity: Impact on atherosclerosis. Phytother. Res. 2021, 35, 2854–2878.
120. Finley, J.W.; Burrell, J.B.; Reeves, P.G. Pinto bean consumption changes SCFA profiles in fecal fermentations, bacterial populations of the lower bowel, and lipid profiles in blood of humans. J. Nutr. 2007, 137, 2391–2398.
121. Taga, M.S.; Miller, E.E.; Pratt, D.E. Chia seeds as a source of natural lipid antioxidants. J. Am. Oil Chem. Soc. 1984, 61, 928–931.
122. Ayerza, R. The seed's oil content and fatty acid composition of chia (Salvia hispanica L.) Var. Iztac 1, grown under six tropical ecosystems conditions. Interciencia 2011, 36, 620–624.
123. Ciftci, O.N.; Przybylski, R.; Rudzińska, M. Lipid components of flax, perilla, and chia seeds. Eur. J. Lipid Sci. Technol. 2012, 114, 794–800.
124. Carrero, J.J.; Martín-Bautista, E.; Baró, L.; Fonollá, J.; Jiménez, J.; Boza, J.J.; López-Huertas, E. Efectos cardiovasculares de los ácidos grasos omega-3 y alternativas para incrementar su ingesta. Nutr. Hosp. 2005, 20, 63–69.
125. Kritchevsky, D. Conjugated linoleic acid in experimental atherosclerosis. In Advances in Conjugated Linoleic Acid Research; AOCS Publishing: New York, NY, USA, 2020; Volume 2, pp. 292–301.
126. Kritchevsky, D.; Tepper, S.A.; Wright, S.; Czarnecki, S.K.; Wilson, T.A.; Nicolosi, R.J. Conjugated linoleic acid isomer effects in atherosclerosis: Growth and regression of lesions. Lipids 2004, 39, 611–616.
127. Wilson, T.A.; Nicolosi, R.J.; Chrysam, M.; Kritchevsky, D. Conjugated linoleic acid reduces early aortic atherosclerosis greater than linoleic acid in hypercholesterolemic hamsters. Nutr. Res. 2000, 20, 1795–1805.

128. Anderson, J.W.; Smith, B.M.; Washnock, C.S. Cardiovascular and renal benefits of dry bean and soybean intake. Am. J. Clin. Nutr. 1999, 70, 464S–474S.

129. Glore, S.R.; Van Treeck, D.; Knehans, A.W.; Guild, M. Soluble fiber and serum lipids: A literature review. J. Am. Diet. Assoc. 1994, 94, 425–436.

130. Kritchevsky, D. Protein and atherosclerosis. J. Nutr. Sci. Vitaminol. 1990, 36, S81–S86.

131. Navab, M.; Anantharamaiah, G.; Hama, S.; Garber, D.W.; Chaddha, M.; Hough, G.; Lallone, R.; Fogelman, A.M. Oral administration of an Apo AI mimetic peptide synthesized from D-amino acids dramatically reduces atherosclerosis in mice independent of plasma cholesterol. Circulation 2002, 105, 290–292.

132. Wang, S.; Wu, D.; Matthan, N.R.; Lamon-Fava, S.; Lecker, J.L.; Lichtenstein, A.H. Reduction in dietary omega-6 polyunsaturated fatty acids: Eicosapentaenoic acid plus docosahexaenoic acid ratio minimizes atherosclerotic lesion formation and inflammatory response in the LDL receptor null mouse. Atherosclerosis 2009, 204, 147–155.