Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 9 Issue 5 May 2025

Review Article

Pathophysiological Approach to the Development of Plant Compositions with 'Anti-Age' Activity

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DOI: 10.31080/ASMS.2025.09.2075

Received: March 17, 2025

Published: April 16, 2025

Abstract

For the prevention of stroke, myocardial infarction, metabolic syndrome, and type II diabetes, biologically active dietary supplements containing plant extracts are among the most promising options. These dietary supplements can be used from the age of 25-30, as they are safe and do not exhibit significant dose-dependent side effects. The key aspect of developing such a biologically active dietary supplement is selecting the most effective plant extracts that, on one hand, provide mild hypoglycemic and hypocholesterolemic effects and moderately lower blood pressure, while on the other hand, ensure that their effects remain within the physiological norm for a healthy individual. To achieve this, a dietary supplement composition was developed based on plant extracts from Bergamot fruit, Wild Yam, Barberry fruit, and *Peruvian Maca*. This phytocomposition was formulated based on existing data on the physiological effects of these plant extracts. Considering the primary and additional activities of the components in the developed dietary supplement, it may provide comprehensive preventive effects against various age-related pathological processes.

Keywords: Prevention; Biologically Active Dietary Supplement; Plant Extracts; Bergamot; Wild Yam; Barberry; *Peruvian Maca*

Introduction

Currently, compensating for age-related changes and developing drugs with 'anti-age' activity is one of the most pressing challenges in modern medicine. This urgency arises from two factors: the emergence of new data on the molecular and cellular mechanisms of aging and the steady increase in the aging population, particularly in economically developed countries. Together, these factors have strongly driven the search for highly effective 'anti-age' treatments. While the dominant role in developing 'anti-age' products has traditionally belonged to cosmetology, in recent years, there has been a growing demand for systemic drugs and orally administered biologically active dietary supplements designed for both compensation and, especially, prevention of age-related changes. In this context, biologically active dietary supplements with plant-based components are of particular interest, as their effects target key pathophysiological mechanisms of the aging process [1].

Aging is a natural process accompanied by functional impairments in many body systems. With age, the prevalence of cardiovascular diseases increases, including atherosclerosis, ischemic heart disease, arterial hypertension, myocardial infarction, stroke, and type 2 diabetes (T2D). Diseases of the musculoskeletal system such as arthritis, osteoporosis, and sarcopenia also become more common, and men may develop hypogonadism, all of which significantly limit physical capabilities [2].

Among the key pathophysiological mechanisms of aging, the most significant include atherosclerosis, metabolic syndrome (leading to hypertension, type II diabetes, and obesity combined with hormonal imbalances), and age-related androgen deficiency. These pathological processes ultimately cause critical vascular endothelial damage, such as stroke and myocardial infarction, which remain leading causes of mortality worldwide [3].

Published data from the 2015 Global Burden of Disease (GBD) project indicate that 10.3 million stroke cases occur annually, with 6.5 million resulting in death [4]. To quantify the burden of stroke, the measure of Disability-Adjusted Life Years (DALYs) is widely used, with a global impact estimated at 113 million years lost annually [5].

In addition to these conditions, the prevalence of age-related pathologies such as cancer and neurodegenerative diseases (e.g., Parkinson's and Alzheimer's) is increasing. Despite differences in their pathogenesis—particularly in oncology—mortality is frequently caused by damage to vital organs (heart, brain, liver, and kidneys) due to critical vascular endothelial injuries and tissue ischemia. Consequently, a crucial direction in modern biogerontology is the development of biologically active dietary supplements with comprehensive preventive effects, aiming to prevent ischemic vascular damage in the heart and brain, hypertension, and type II diabetes at an early stage.

A fundamentally new concept for stroke and myocardial infarction prevention is actively being developed. This approach focuses on a slight, sustained reduction in blood pressure, blood glucose levels, and cholesterol levels. Studies have shown that reducing blood pressure by 5–10 mmHg, blood glucose by 0.2–0.4 units, and cholesterol by 2–5 units lowers the risk of stroke and myocardial infarction by more than 10%. Moreover, the earlier such preventive measures are implemented, the greater the reduction in risk [6].

However, finding pharmacological agents suitable for such preventive use has proven challenging. Most pharmaceutical drugs, from ACE inhibitors and statins to hypoglycemic agents, have significant side effects, primarily hepatotoxicity (liver cell damage). These drugs are intended for specific indications and contraindications, making them unsuitable for long-term preventive use in individuals with risk factors but no diagnosed disease.

In this regard, biologically active dietary supplements containing plant extracts are among the most promising options for preventing stroke, myocardial infarction, and type II diabetes. These supplements can be used as early as 25–30 years of age, as they are completely safe and do not exhibit significant dose-dependent side effects. The key challenge in developing such supplements lies in selecting the most effective plant extracts that provide mild hypoglycemic and hypocholesterolemic effects while moderately lowering blood pressure. At the same time, their effects must remain within the physiological norm for a healthy individual.

To prevent stroke, myocardial infarction, and type II diabetes, a biologically active dietary supplement was developed based on plant extracts from Bergamot fruit, Wild Yam, Barberry fruit, and *Peruvian Maca*. This phytocomposition was formulated based on existing data on the physiological effects of these plant extracts. The plant components of the dietary supplement have the following proven properties.

Bergamot fruit extracts

Bergamot is a type of citrus fruit grown in southern Italy. Its fruits and leaves contain polyphenols, carotenoids, flavonoids, and terpenoids, which have potential therapeutic effects on various pathological processes.

Clinical trials have shown that in patients with hypercholesterolemia, different forms of orally administered Bergamot can reduce total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels [7]. All studies consistently reported good tolerability, with study durations ranging from 30 days to 12 weeks.

For example, the intake of Bergamot Juice Extract (BJe) in a fixed dose (150 mg flavonoids daily for six months) in individuals with moderate hypercholesterolemia (LDL-C plasma levels of 4.1–4.9 mmol/L) led to statistically significant reductions in total cholesterol (TC) (from 6.6 to 5.8 mmol/L), triglycerides (TG) (from 1.8 to 1.5 mmol/L), and LDL-C (from 4.6 to 3.7 mmol/L), while high-density lipoprotein cholesterol (HDL-C) increased from 1.3 to 1.4 mmol/L [12]. Therefore, BJe intake lowers plasma lipid levels

and improves the lipoprotein profile, reducing cardiometabolic risk in patients with dyslipidemia.

A positive effect was observed with Bergamot Polyphenolic Fraction (BPF) at daily doses of 500 mg or 1000 mg for 30 days [13], leading to reductions in TC, LDL-C, and TG while increasing HDL-C. Similar results were obtained with oral intake of 1000 mg BPF per day in another study [8].

Bergamot polyphenols improve health, particularly in metabolic disorders associated with obesity, such as insulin resistance, type II diabetes (T2D), and cardiovascular diseases [15]. These benefits are achieved through direct and indirect regulation of various target proteins involved in inflammatory signaling pathways.

A study examined patients with metabolic syndrome (MS) following a Mediterranean diet and taking a phytocomplex with BJe. The results showed that the phytocomplex enhanced the beneficial effects of the diet, as evidenced by improvements in metabolic syndrome severity markers (TC, LDL-C, HDL-C, TG, and glucose) and inflammatory markers such as C-reactive protein (CRP) [9].

A similar effect was observed with a nutraceutical containing Bergamot extract. In overweight individuals with dyslipidemia, systemic inflammation was reduced, with significant decreases in high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-alpha (TNF-α).

The hypolipidemic effect of Bergamot has also been demonstrated in several experimental studies. In rats fed a high-fat diet with BPF supplementation, there was a reduction in TC, LDL-C, TG, and fasting glucose levels, along with the normalization of Apolipoprotein A1 (Apo A1) and Apolipoprotein B (Apo B) levels. Additionally, HDL-C levels increased compared to rats that consumed only the high-fat diet [10]. BPF use also significantly reduced thiobarbituric acid-reactive substances (TBARS), indicating that Bergamot polyphenols help prevent diet-induced lipid profile disturbances and counteract oxidative stress.

A study [11] demonstrated the therapeutic efficacy of Bergamot Powdered Juice (PBJ), which contains fiber from the solid parts of the fruit remaining after juice extraction. In an *in vivo* model of metabolic syndrome in rats induced by a high-sugar and high-fat (HSF) diet, significant increases in blood glucose, TG, insulin resistance, systolic blood pressure (SBP), visceral fat, and body mass index (BMI) were observed. Interestingly, PBJ administration did not affect these parameters in control rats, but it significantly improved them in HSF-fed rats. The beneficial effects of PBJ are attributed to both Bergamot polyphenols, which exhibit anti-inflammatory, antioxidant, and lipid-regulating properties, and its dietary fiber and non-phenolic components, such as stachydrine.

In a metabolic syndrome (MS) model induced by an HSF diet in male Wistar rats, intragastric administration of Bergamot Leaf Extract (BLE) reduced oxidative stress and inflammation levels in adipose tissue, heart, liver, and kidneys, as well as decreased triglyceride (TG) levels, insulin levels, and insulin resistance [12]. BLE administration affects all target organs in obesity, improving redox balance and inflammation in diet-induced MS.

The Bergamot Polyphenolic Fraction (BPF), when added to the diet of Wistar rats with diet-induced hyperlipidemia, improved serum parameters. BPF intake also had a positive impact on MS treatment in patients with hyperlipidemia and/or hyperglycemia.

There is evidence demonstrating the beneficial effects of Bergamot when combined with other phytoextracts. One study showed that a dose of 250 mg of Bergamot fruit extract combined with 110 mg of a mixture of nine other phytoextracts reduced TC, LDL-C, and Apo B levels in patients with moderate cardiometabolic risk factors [21].

In an experiment on rabbits subjected to heat stress (27–30ºC), researchers investigated the effects of Bergamot Oil Nano-Emulsion (NBG). The groups receiving NBG at 50 and 100 mg/kg body weight had lower levels of total and direct bilirubin, TG, LDH, creatinine, and amyloid A, while showing significantly increased levels of nitric oxide, IgA, IgM, total antioxidant capacity (TAC), and superoxide dismutase (SOD) compared to the control group that received only water [13]. The group receiving the higher NBG dose had the highest levels of total protein, albumin, GPx, T3, and T4, along with the lowest levels of uric acid, MDA, and indirect bilirubin. Both treated groups showed significantly lower levels of 8-OHdG, amyloid A, and TLR4, while significantly increasing nitric oxide, IgA, IgM, TAC, and SOD. These findings suggest that oral administration of NBG enhances rabbits' heat tolerance, primarily due to its antioxidant and anti-inflammatory effects.

Due to the close relationship between aging and oxidative stress, functional foods rich in phytochemicals serve as excellent agents for counteracting age-related changes [23]. In a human erythrocyte aging model exposed to D-galactose for 24 hours, pre-incubation with Bergamot peel and juice extract was shown to prevent the formation of reactive oxygen species (ROS), thereby reducing oxidative stress and preventing damage to biological macromolecules, including membrane lipids and proteins. Bergamot extracts prevented excessive activation of endogenous antioxidant enzymes, such as catalase and SOD, and inhibited the activation of glucose-6-phosphate dehydrogenase, which shifts erythrocyte metabolism from glycolysis to the pentose phosphate pathway. The study suggests that Bergamot peel and juice extract may neutralize age-related erythrocyte changes due to its rich composition of bioactive compounds that target aging and oxidative stress.

Photoaging is a combination of intrinsic aging and damage caused by chronic exposure to ultraviolet (UV) radiation, contributing to most age-related skin appearance changes. It has been demonstrated that BPF can inhibit UV-induced suppression of keratinocytes, prevent the overexpression of the pro-inflammatory cytokine biomarker interleukin-1 beta (IL-1β), delay telomere shortening, and maintain telomerase activity, thereby preventing UV-induced skin aging [24].

A study [24] demonstrated that BPF protects human keratinocytes from UV-induced oxidative stress and photoaging markers in a dose-dependent manner, suggesting its potential as a beneficial addition to skincare products. Alongside its antioxidant properties, Bergamot polyphenols appear to modulate key cellular signaling pathways, leading to anti-proliferative, rejuvenating, and immunomodulatory responses.

A review conducted by a group of authors [14] highlighted that Bergamot is a rich source of flavonoids, which provide a broad spectrum of anti-inflammatory properties. The anti-inflammatory effects of Bergamot juice extract were demonstrated in experimental models of acute inflammation induced by lipopolysaccharide exposure (*in vitro* on monocytes and *in vivo* in rats). It was shown that inhalation of Bergamot Essential Oil (BEO) in mice with ovalbumin-induced allergy reduced lung inflammation and airway narrowing by decreasing the levels of IL-4, IL-5, IL-13 (both at gene and protein levels), IL-6, IL-1β, and TNF-α, while also inhibiting collagen deposition.

An example of the anti-inflammatory effects of Bergamot derivatives is found in the treatment of anal/proctological inflammation using Bergamot oil. Bergamot flavonoids, including hesperidin, naringenin, and apigenin, exhibit anti-inflammatory properties, reduce local bleeding and hyperemia, and promote rapid wound healing.

Thus, Bergamot phytochemical compounds exhibit both preventive and therapeutic properties for various systemic diseases, primarily due to their anti-inflammatory and antioxidant activities and their role in regulating metabolic processes in the body.

Wild Yam (Dioscorea) extracts

Dioscorea, commonly known as Chinese Yam, is a perennial plant belonging to the Dioscoreaceae family. It is widely cultivated in China as a functional food and a natural medicinal product.

The beneficial properties of Dioscorea are attributed to its phytochemical compounds, particularly polysaccharides, saponins, flavonoids, dehydroepiandrosterone, and allantoin.

Saponins are a class of high-molecular-weight glycosides derived from triterpenoids or steroids. Depending on their structural differences, they are classified into steroidal and triterpenoid saponins. These compounds exhibit numerous pharmacological properties, including anti-inflammatory, antioxidant, anti-apoptotic, anti-diabetic, anti-cancer, and neuroprotective effects. Additionally, saponins demonstrate immunostimulatory, hypocholesterolemic, hypoglycemic, antifungal, and cytotoxic properties [15].

A higher concentration of compounds has been found in the peel of yam tubers compared to the pulp. The pulp contains high levels of dehydroepiandrosterone (DHEA), whereas allantoin and flavonoids are more abundant in the peel.

Diosgenin and dioscin, the main steroidal saponins found in Dioscorea, have been shown to relax muscles and activate blood circulation [36]. Their cardioprotective effects are associated with inhibiting inflammation, regulating myocardial energy metabolism

disorders, and providing anti-ischemic and anti-apoptotic actions [16].

Dioscin has been reported to protect the heart from hypertrophy induced by angiotensin II, reducing cell size, protein content, reactive oxygen species (ROS) levels, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and β-myosin heavy chain (β-MHC). Additionally, dioscin lowers creatine phosphokinase, malondialdehyde (MDA), and lactate dehydrogenase levels, while increasing glutathione, superoxide dismutase (SOD), and glutathione peroxidase, thereby counteracting oxidative stress.

Dioscorea polysaccharides and diosgenin exhibit anti-hypoxic effects through a mechanism dependent on hypoxia-inducible factor-1α (HIF-1α), mRNA expression, and vascular endothelial growth factor A (VEGF-A) protein expression, thus stimulating angiogenesis under hypoxic conditions. Dioscorea polysaccharides have also demonstrated neuroprotective effects against hypoxia-induced neuronal apoptosis [17].

Several studies have investigated the role of Dioscorea phytochemicals in lipid metabolism regulation and obesity control. The inclusion of polysaccharides extracted from *Dioscorea opposita* in the diet of mice fed a high-fat diet resulted in weight loss, reduced adipose tissue, improved insulin resistance (IR), and decreased inflammation [18]. These effects were attributed to Dioscorea polysaccharides, which reduce systemic inflammation and improve gut microbiota composition in obese mice.

Another study found that Sprague Dawley rats fed a high-fat diet along with methanolic extract of Dioscorea nipponica Makino powder had lower body weight and adipose tissue mass compared to control rats that consumed only a high-fat diet [19]. These results were linked to *Dioscorea saponins* (dioscin and diosgenin), which inhibited blood triacylglycerol absorption when administered orally with corn oil, suggesting their fat absorption inhibitory effects.

Significant reductions in total cholesterol (TC), LDL-C, lipase, fasting blood glucose, and body weight, along with an increase in HDL-C and ghrelin levels, were observed in Wistar rats with diet-induced obesity following treatment with Dioscorea bulbifera extract at doses of 200 mg/kg and 400 mg/kg for six weeks, compared to the negative control group (rats receiving water) [20]. The observed lipase inhibition suggests that Dioscorea may be a promising natural anti-obesity agent.

Another steroidal saponin, trillin, isolated from Dioscorea nipponica Makino rhizome, exhibited strong antihyperlipidemic activity [15]. Administration of an ethanolic Dioscorea extract in high-fat diet-fed rats led to lower TC and triglyceride (TG) levels while restoring normal HDL-C and LDL-C levels.

In an experiment on diabetic rats, administration of Dioscorea esculenta improved glycemic control by activating the glucose transporter type 4 (GLUT-4) signaling pathway and increasing sex steroid hormone levels in muscles.

In an aging model induced by daily D-galactose injections in rats, oral administration of diosgenin (0, 10, or 50 mg/kg/day) for eight weeks prevented age-related bone loss. These results suggest a positive effect of diosgenin on osteoporosis in older adults [47]. The authors also observed reduced porosity, increased cortical bone area, and higher bone mineral density compared to rats receiving a placebo [21].

It is known that with age, the amount of fat and fibrous connective tissue in muscles increases, leading to muscle mass loss and reduced muscle function. It has also been established that physical exercise can enhance muscle fiber quantity and function while reducing muscle fibrosis [50,51]. However, for elderly individuals, regular physical exercise may not always be feasible due to physical limitations, time constraints, or other factors.

Studies have shown that Dioscorea esculenta tablets (2000 mg/day) combined with low-intensity strength exercises for 12 weeks were more effective at improving muscle quantity and quality in middle-aged and older adults than exercise alone without Dioscorea esculenta supplementation [22].

Additionally, consuming Dioscorea esculenta tablets (2000 mg/day) combined with strength training further increased muscle mass and strength by enhancing androgen secretion in athletes. This phenomenon may be explained by the fact that diosgenin, found in Dioscorea, is a plant-derived steroidal saponin with a molecular formula similar to dehydroepiandrosterone (DHEA) [23].

There is evidence that DHEA, a precursor of steroid hormones, is metabolized into testosterone via steroidogenic enzymes, such as 3β-hydroxysteroid dehydrogenase (HSD) and 17β-HSD, and that testosterone is further converted into the physiologically active hormone dihydrotestosterone (DHT) via 5α-reductase in skeletal muscles. This indicates the possibility of sex steroid hormone synthesis within skeletal muscles. It is known that androgenic hormones play a key role in increasing muscle glucose uptake, lipid metabolism, and muscle protein synthesis. However, with age, the ability to secrete sex steroid hormones declines.

Regular strength training increases muscle mass, androgen hormone expression, and steroidogenic enzyme activity in older adults, and elevated muscle DHT secretion correlates with muscle hypertrophy [23]. Additionally, rodent models have confirmed that resistance training induces muscle hypertrophy and improves glycemic control, whereas DHT inhibitor treatment suppresses these effects. These findings emphasize the importance of resistance training in preserving muscle mass and preventing sarcopenia in the elderly.

In a post-traumatic stress disorder (PTSD) model, where BALB/c mice were subjected to two hours of restraint, followed by 20 minutes of forced swimming and 15 minutes of rest, diosgenin was administered in three doses (20, 40, and 60 mg/kg). The study results demonstrated that diosgenin alleviated anxiety and depressive behavior, improved cognitive functions, restored monoamine and vitamin C levels in a dose-dependent manner, and regulated adenosine and its metabolites in specific brain regions [24]. Additionally, the authors observed a restoration of elevated corticosterone levels in serum.

Thus, Dioscorea, due to its rich phytochemical composition, exhibits antioxidant, anti-diabetic, anti-hyperlipidemic, anti-inflammatory, and neuroprotective properties.

Barberry fruit extracts

Barberry - *Berberis* spp. is a shrub of the Berberidaceae family and comprises about 500 species, which are commonly grown in Europe, the USA, South Asia, and some northern regions of Iran and Pakistan [61]. It is used in folk and traditional medicine, and some of its parts, such as roots, bark, stem, shoots, leaves, and fruits, are used as components of pharmacological therapy.

The most important compounds of barberry are alkaloids (berberine and others), triterpenoids, and phytosterols [25], phenolic acids, flavonoid glycosides, flavonoid aglycones, the quality and quantity of which vary depending on the type of extracts obtained from flowers, leaves, fruits, or stems.

Currently, research on barberry has sparked renewed interest in this species, mainly due to its valuable fruits, which are a source of nutrients and a preventive agent [65]. Barberry fruits contain carotenoids, flavonoids, phenolic compounds, anthocyanins, and some alkaloids, various minerals (calcium, iron, potassium, phosphorus, sodium, copper, zinc, manganese, magnesium, phosphorus), as well as vitamins (ascorbic acid, vitamin K) [62]. The literature describes numerous clinical and experimental studies demonstrating a wide range of beneficial properties of barberry and its biologically active components. Their use in monotherapy or in combination with other substances allows achieving positive effects in both humans and animals [26].

When berberine is consumed by adults, a significant reduction in the waist-to-hip ratio has been observed. There is evidence that berberine significantly reduces waist circumference but does not affect body weight, body mass index, or the waist-to-height ratio [27]. At the same time, when evaluating the “dose-effect” relationship, it has been established that berberine intake significantly reduces BMI (r = -0.02) and WHR (r = -0.72) depending on the duration of treatment.

In an *in vitro* study, the addition of 8 μM berberine can almost completely suppress the induction of adipogenesis and reduce the levels of mRNA and proteins associated with SREBP-1 (sterol regulatory element binding protein-1) [28].

It has been shown that berberine suppresses adipocyte differentiation and reduces obesity levels. In another study [29], it was noted that berberine reduces lipid droplet deposition in preadipocytes and suppresses the terminal differentiation of adipocytes. This mechanism is associated with the suppression of PPAR-γ2 mRNA expression, leading to a decrease in TG levels and lipid stores.

Thus, berberine and potentially alkaloid-enriched plant extracts can reduce: 1) adipocyte differentiation, 2) intracellular neutral

lipids and cholesterol content, 3) lipolysis, 4) fatty acid uptake, 5) intracellular lipid metabolism in LDS, and 6) lipid droplet (LD) mobility, indicating its ability to influence lipid metabolism.

It has been shown that the consumption of 3 g of B. vulgaris fruit extract per day for 3 months in patients with type 2 diabetes significantly reduced the levels of TG, TC, LDL-C, and apoB in the serum [30]. The extract of B. vulgaris fruits significantly reduces the levels of LDL-c/HDL-c, TG/HDL-c, TC/HDL-c, and apoB/apoA-I. The ratio of LDL-C/HDL-C is a well-known risk factor for cardiovascular diseases, and an increase in the LDL-C/HDL-C ratio is associated with an elevated risk of cardiovascular diseases.

Taking three capsules of barberry extract (200 mg/day for 6 weeks) by patients with metabolic syndrome significantly reduces the levels of heat shock proteins (anti-HSP 27 and 60), high-sensitivity CRP, and improves the lipid profile (decrease in TC, LDL-C, and increase in HDL-C) [31].

A meta-analysis of five randomized controlled trials involving 339 participants showed that berberis extract supplements significantly reduced levels of TC, TG, and LDL-C, while changes in HDL-C levels were not statistically significant [29]. Improvement in condition with berberine intake at dyslipidemia with an effect on the low-density lipoprotein receptor [32] was accompanied by an increase in HDL-C levels [33].

The results of clinical studies also show that barberry extracts have a beneficial effect on blood pressure, inflammation, and lipid profile [32].

The review [26] describes several mechanisms by which berberine is capable of lowering cholesterol levels, namely, the reduction of PCSK9 expression and, consequently, the decrease in LDL receptor degradation, which stimulates the uptake of cholesterol from plasma by the liver and promotes the removal of LDL cholesterol from the blood and its entry into bile. It also directly affects LDL receptor expression and induces receptor activation by stabilizing their mRNA (activation of kinases regulated by extracellular signals). Berberine also reduces cholesterol absorption in the intestine, increases its excretion in feces, and promotes cholesterol metabolism in the liver and bile acid production. Furthermore, it stimulates AMP-activated protein kinase, which can limit fatty acid synthesis. There is evidence that berberine may reduce TG synthesis [34].

Berberis extracts are capable of activating gene transcription factors as they are synthetic ligands for peroxisome proliferator-activated receptor alpha (PPAR-α), which is known as a ligand-activated transcription factor and is a member of the nuclear hormone receptor superfamily [29]. It is predominantly expressed in tissues (liver, heart, kidneys, muscles) that metabolize fatty acids. Activation of PPAR-α reduces TG levels and increases HDL-C levels in serum.

In a double-blind randomized clinical trial involving 31 patients with type 2 diabetes using barberry fruit extract, a significant reduction in serum glucose and insulin levels was observed [30]. Administration of 25 mg/kg and 62.5 mg/kg of saponin extract and aqueous barberry extract to rats with streptozotocin-induced diabetes from the first day of administration reduced blood glucose levels by more than 70% compared to the control group.

Activation of the hypothalamic-pituitary-adrenal axis is closely associated with insulin resistance, disturbances in glucose and lipid metabolism in type 2 diabetes [35]. In an animal experiment, it was proven that berberine (200 mg/kg) significantly reduced fasting blood glucose levels by altering the lipid profile. It also improved the levels of HDL cholesterol, insulin resistance index, insulin sensitivity index, glucagon, and insulin. Berberine reduces the levels of orexin-A in the hypothalamus, OX2R receptor, corticotropin-releasing hormone, adrenocorticotropic hormone in the pituitary and plasma, and corticosterone in serum and urine. At the same time, it increases the expression of mRNA and GLUT4 protein in the skeletal muscles of the experimental rats.

It has been shown that barberry extract reduces postprandial hyperglycemia (HbA1c) by inhibiting the activity of the α-glucosidase enzyme.

In a randomized double-blind placebo-controlled clinical trial involving patients with metabolic syndrome, it was shown that the administration of berberine hydrochloride (500 mg) three times a day before meals for 3 months leads to remission of metabolic syndrome (36%) and a reduction in waist circumference, systolic blood pressure, triglyceride levels, and total insulin secretion, and importantly, an increase in insulin sensitivity [36].

The accumulation of white adipose tissue and inflammation contribute to obesity, causing insulin resistance [37]. Thus, in mice with diet-induced obesity, combined treatment with berberine

reduced obesity and dyslipidemia in the animals, improved glucose tolerance and insulin resistance, and reduced the accumulation and infiltration of M1 macrophages in adipose tissue. In another study, it was shown that berberine suppresses the phosphorylation of IRS-1 (Ser307) in adipose tissue and cultured adipocytes. However, AKT (Ser473) phosphorylation was increased in adipose tissue treated with berberine. The conditioned medium from adipocytes treated with berberine reduced the number of infiltrating macrophages. Thus, berberine partially restored the impaired glucose uptake and IRS-1 (Ser307) activation in adipocytes caused by macrophage activation.

A meta-analysis showed that berberine extract supplements significantly reduce insulin levels, while other glycemic indicators may not change (fasting blood sugar concentration, HOMA-IR, HbA1c). In the study [38] involving patients with diabetes type 2 who consumed barberry fruits for 8 weeks, a significant decrease in serum glucose levels to 136.15 ± 32.8 mg/dL and a reduction in HbA1c levels to 7.07 ± 1.21 mg/dL were observed. Thus, berberine extracts may improve glucose catabolism via the glycolytic pathway, stimulate insulin secretion, or enhance insulin function, and finally, reduce glucose absorption.

The combined use of barberry in D-galactose-induced rat aging models restored the levels of pro- and antioxidants in erythrocytes. Berberine also restored the activity of Na+/K+-ATPase and Ca2+ ATPase in the erythrocyte membrane. Based on these results, the authors [39] suggested that berberine treatment could slow down erythrocyte aging in rats by stabilizing the redox balance.

The extract of barberry, depending on the concentration, increased lifespan by up to 6%, contributed to health improvement (stress resistance by up to 35%, motor activity by up to 25%, intestinal barrier integrity by up to 12%, metabolism rate by up to 5%) in Drosophila melanogaster. The authors showed that lower concentrations of barberry extract increased the stress resistance of females, while higher concentrations negatively affected the stress resistance of males, thereby highlighting the complex dynamics of the influence of dose and sex on the modulation of the stress response. *Berberis* extracts and berberine can suppress the production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-17) and enhance the expression of anti-inflammatory cytokines (IL-10, TGF-β) in various cell types and tissues. They also suppress the activation of inflammatory signaling pathways such as NF-κB, MAPK, JAK/STAT, and AP-1.

Meta-analyses have shown a positive effect of berberine supplements on the concentration of IL-6, TNF-α, and CRP in serum. It is capable of reducing elevated levels of TNF-α, IL-6, and MCP-1 in serum, as well as the expression of TNF-α, IL-6, and MCP-1, and attenuating the phosphorylation of JNK and IKKβ and the expression of NF-κB p65 in adipose tissue during obesity, in Raw264.7 macrophages and 3T3-L1 adipocytes, respectively. Barberry fruit extract significantly increases the overall antioxidant capacity in patients with type 2 diabetes [30].

In a number of studies, it has been demonstrated that berberine is involved in oxidative stress by absorbing free radicals (hydroxyl radical (OH), superoxide anion (O2−), hydrogen peroxide (H2O2), nitric oxide (NO)) and chelating metal ions (Fe2+ and Cu2+).

Berberis extracts and berberine can neutralize free radicals, increase the levels of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, and reduce lipid peroxidation and DNA damage [32].

In animal models, it has been shown that berberine restores the balance of pro- and antioxidants by controlling the levels of MDA, protein carbonyl compounds, protein peroxidation products, and reduced glutathione (GSH), thiols, and the ferric reducing ability of plasma (FRAP) in erythrocytes or plasma [40].

There is evidence that berberine effectively reduces doxorubicin-induced oxidative stress by decreasing the production of ROS, MDA, mitochondrial damage, and increasing SOD, activating the Nrf2-mediated pathway, thereby preventing diastolic heart dysfunction and fibrosis by inhibiting the differentiation of cardiac fibroblasts into myofibroblasts, reducing the expression of α-smooth muscle actin (α-SMA), collagen I, and collagen III in cardiac fibroblasts. The high antioxidant activity of the barberry extract is also evidenced by the statistically significant reduction in the metHb/oxyHb and ferrylHb/oxyHb ratios in erythrocytes in its presence.

Barberry extracts contain vasodilatory substances, including berberine, which affect blood pressure levels by regulating the central nervous system. In a study involving 46 patients with diabetes type 2, 23 of whom consumed 200 ml of barberry fruit

juice daily for 8 weeks, a significant reduction in systolic blood pressure, diastolic blood pressure, fasting blood sugar levels, and levels of total cholesterol and triglycerides was observed, while the concentration of paraoxonase-1 (PON1) increased.

In a randomized, placebo-controlled, double-blind study, 60 patients with MS were enrolled, taking either *berberis* extract or placebo (550 mg/day for 3 weeks) [41]. At the end of the treatment, the experimental group showed a significant reduction in SBP, waist circumference, hematocrit, and serum LDL levels. In a randomized controlled parallel study of patients with hypertension of both sexes, who took barberry extract (10 g per day) for 8 weeks, an improvement in brachial flow-mediated dilation and a positive effect on the levels of intracellular adhesion molecule-1 and macrophage/monocyte chemo-attractant protein-1 in plasma were observed [42].

There are other cardiovascular mechanisms of action of berberine described in the literature, namely, inhibition of ACE activity and direct release of NO/cGMP from the endothelium. Enhancement of K+ currents and inhibition of intracellular Ca+2 release. Berberine promotes the reduction of Na+ reabsorption in the kidneys, which can also lead to a decrease in blood pressure. Since hypertension is a major risk factor for cardiovascular diseases, including myocardial infarction, cerebrovascular diseases, heart failure, and chronic kidney diseases, the potential for controlling blood pressure with barberry extracts is very promising.

Barberry extract successfully reduces both acute and chronic pain by activating opioid receptors [32]. Barberry extracts and the berberine they contain exert immunomodulatory effects in various immune disorders: allergic reactions, autoimmune diseases, and others.

It is known that berberine exerts a strong antitumor effect in many types of cancer, such as oral cavity cancer, bone cancer, skin cancer, breast cancer, cervical and endometrial cancer, thyroid cancer, bladder cancer, stomach cancer, liver cancer, colorectal cancer, prostate cancer, and cell lines of lung, liver, breast, kidney cancer, leukemia [43]. The antitumor effect is associated with the suppression of proliferation, induction of apoptosis and autophagy, as well as the inhibition of angiogenesis and metastasis. According to the studies presented in the review [43], berberine affects several intracellular targets involved in the cell cycle, apoptosis, and various signaling pathways. It has been shown to regulate Fas, ROS, and p53 (tumor suppressor protein) dependent apoptosis signaling pathways by increasing the levels of Fas receptor (death receptor)/FasL (Fas ligand), ROS, ATM, p53, retinoblastoma protein (Rb), caspases-9, 8, 3, TNF-α, Bcl2-associated X protein (Bax), BID, and decreasing Bcl2, Bcl-X, c-IAP1 (inhibitor of apoptosis protein), X-linked inhibitor of apoptosis protein (XIAP), and survivin levels. Moreover, berberine affects the expression of several proteins that play an important role in the cell cycle of tumor cells, including Cyclin-D1, Cyclin-B1, Cdc25, CDK1, Wee1, Cip1/p21 (cyclin-dependent kinase inhibitor 1), ZO-1, Kip1/p27, NF-kappaB, epidermal growth factor (EGF), Raf/MEK/ERK, platelet-derived growth factor (PDGF), activator protein-1 (AP-1), AP-2, CD147, and PI3K/Akt. It also suppresses the expression of MMP-2 and MMP-9. Thus, berberine may inhibit metastasis and migration in various types of cancer, as MMPs play an important role in the migration of tumor cells leading to metastasis.

There is data on the effects of berberine derivatives on microorganisms and fungi. In particular, the antimicrobial effect of barberry extract has been described against *Streptococcus sobrinus, Streptococcus sanguinis*, *Streptococcus salivaris*, *Lactobacillus rhamnosus*, as well as against *Staphylococcus aureus*, *Enterococcus faecalis*, and various species of *Candida, Staphylococcus aureus* ATCC9973, *Escherichia coli* HB101, *Staphylococcus enteritis*, *Escherichia coli* Cip812, and *Penicillium verrucosum*, *Fusarium proliferatum*, *Aspergillus ochraceous*, *Aspergillus niger*, *Aspergillus flavus* [44].

In an *in vitro* study, it was shown that the tested plant extracts of barberry and berberine exhibited antibacterial activity against Helicobacter pylori. At the same time, the authors note that the activity of the extracts was lower than that of berberine. Antibacterial activity against other bacteria, including *Actinobacillus pleuropneumoniae* L. [26], *Shigella dysenteriae* L., and *Streptococcus agalactiae* L. [45], has been described. The antibacterial effect of berberine is explained by its ability to inhibit DNA and protein synthesis, induce cytoplasmic pyknosis, and cause bacterial death. Moreover, it inhibited the synthesis of proteins associated with bacterial growth and division, thereby blocking their reproduction.

Berberine also has an effect on protozoa. There is evidence that it affects *Entamoeba histolytica*, *Giardia lamblia, Trichomonas vaginalis*, *Leishmania donovani.*

Recently, data on the antiviral action of berberine has emerged. It has been shown to reduce viral replication and affect specific interactions between the virus and its host [46]. It integrates into DNA and suppresses DNA synthesis and reverse transcriptase activity, inhibiting the replication of herpes simplex virus (HSV), human cytomegalovirus (HCMV), human papillomavirus (HPV), and human immunodeficiency virus (HIV). It is capable of regulating the MEK-ERK, AMPK/mTOR, and NF-κB signaling pathways, which are necessary for viral replication. Moreover, it has been reported that berberine supports the body's immune response, thereby leading to the destruction of the virus. Since it affects various stages of the virus's life cycle, the authors believe that berberine is a good candidate for use in new antiviral drugs.

Berberine has long been used to treat diarrhea and gastroenteritis [26]. It is effective in treating cholera, capable of suppressing smooth muscle contractions, fluid accumulation in the intestines, and ion secretion, improving conditions in cases of infectious diarrhea and irritable bowel syndrome with diarrhea predominance. These effects are explained by berberine's ability to exert antibacterial, antiviral, and antifungal actions. The literature describes a number of protective effects of barberry and berberine extracts against toxic effects caused by certain chemicals [47].

Side effects of berberine have been reported in some *in vitro* and *in vivo* animal studies, and the observed effects were associated with its neurotoxicity. However, neuroprotective properties of berberine have been demonstrated in animal models of Alzheimer's disease [48]. Intragastric administration of berberine chloride (50 mg/kg/day) for 14 days significantly improved spatial memory and increased the expression of IL-1β and inducible nitric oxide synthase (iNOS) in a rat model of Alzheimer's disease.

It is known that berberine can suppress the effects of addictive substances such as cocaine, morphine (due to the reduction of tyrosine hydroxylase expression), and ethanol. Moreover, it can cross the blood-brain barrier (BBB) and accumulate in the hippocampus, interacting with neurons. Preconditioning with berberine activates endogenous neuroprotective mechanisms associated with the sphingosine-1-phosphate/HIF-1 signaling pathway and helps protect neuronal cells from hypoxia/ischemia [49]. The significant contribution of berberine in various models of neurodegenerative diseases and its mechanisms (PI3K/AKT signaling pathway, AMPK, HIF-1, etc.) are outlined in the review [48,49].

Berberine is capable of exerting anxiolytic effects on behavioral and biochemical indicators associated with anxiety [50]. Thus, in an animal model of post-traumatic stress disorder, it eliminated neurochemical disturbances and the decrease in dopamine levels in the hippocampus and striatum caused by a single prolonged stress. The increased concentration of dopamine during berberine treatment may be partially due to the expression of tyrosine hydroxylase and dopamine transporter mRNA in the hippocampus, while it did not have a significant effect on the expression of vesicular monoamine transporter mRNA in the hippocampus of rats with post-traumatic stress disorder.

The organ-specific action of berberine is due to its ability to distribute in organs and tissues. For example, after oral administration (200 mg/kg), it quickly distributed in the liver, kidneys, muscles, lungs, brain, heart, pancreas, and fat in animals in decreasing order of its quantity [51]. The pharmacokinetic profile showed that the level of berberine in most studied tissues was higher (or much higher) than in plasma four hours after administration. It remained relatively stable in tissues such as the liver, heart, brain, muscles, pancreas, etc. As a result, the concentration of berberine (as well as its bioactive metabolites) in the organs was higher than in the blood after oral administration. This may explain the pharmacological effect of berberine in a range of human diseases.

Maca extracts

The plant *Lepidium meyenii* (maca) is known as *Peruvian maca*, growing in the high-altitude regions of the Andes. Maca has been known for over 2000 years, used as a food product and as a natural remedy, which is why it is called a "superfood". Maca has over 600 varieties, which explains the diversity of the plant's chemical composition and the associated effects.

Maca contains several active components, including alkaloids, glucosinolates, isothiocyanates, polysaccharides, free fatty acids, flavonoids, polyphenols, and sterols, which provide biological activity and nutritional value. The pharmacological value of the plant, associated with the active components, is manifested in the improvement of the anti-stress response, protection against osteoporosis, and anti-tumor activity [52].

The biological and physiological properties of this plant and its impact on the health indicators of the population consuming

maca as food compared to those who do not consume it have been demonstrated [53]. It has been proven that individuals aged between 40 and 75 who consume maca do not show a decrease in the overall health index, assessed through an adapted questionnaire, compared to those residents of the same Andean region who do not use maca as a food product. Furthermore, experiments on rats have shown that red maca extract helps reduce osteoporosis and benign prostatic hyperplasia, while black maca extract increases sperm count, improves memory and learning, and enhances endurance [52]. Maca ensures the preservation of quality of life when used [53].

Having high nutritional value, maca is widely used as a plant supplement for conditions such as sexual dysfunction, decreased sperm quality, and menopausal symptoms [54].

Both methanol and aqueous extracts from dehydrated products of maca exhibited estrogenic activity comparable to that of silymarin in the MCF-7 human breast cancer cell line.

In a clinical study involving 50 Caucasian men suffering from mild erectile dysfunction (ED), those receiving a dry maca extract at a dosage of 2400 mg for 12 weeks noted an improvement in ED and satisfaction profile to a greater extent than men receiving a placebo [55]. The results allow for the recommendation of maca extract for restoring sexual well-being in adult and aging patients with mild ED.

In an experiment feeding 8-week-old (mature) or 18-week-old (adult) male rats with maca extracts for more than six months, an enhancement of the steroidogenic capacity of Leydig cells was observed [56]. The authors suggest that prolonged feeding of male rats with maca extract may enhance the steroidogenic capacity of Leydig cells to slow its decline with age, while in mature male rats, this may only cause a temporary increase in blood testosterone levels.

In a study involving 80 patients with eugonadism and symptoms of late-onset hypogonadism, who took 1000 mg of maca or a placebo (2 tablets 3 times a day for 12 weeks before meals), the scores on the Aging Male Symptoms Scale, International Index of Erectile Function, and International Prostate Symptom Score significantly improved in the maca group compared to the placebo group [57]. The authors believe that maca can be considered an effective and safe treatment for eugonadal patients with symptoms of late-onset hypogonadism.

The use of maca aqueous extract showed improvement in physical performance and endurance in a mouse experiment. The use of maca aqueous extract during fatigue-inducing physical exertion was accompanied by an increase in the grip strength of the mice's paws and endurance during physical activity in the rotating rod test. Moreover, a decrease in blood lactate, blood urea nitrogen, and ROS levels was observed after forced swimming with load. The introduction of the extract strengthens the muscle structures of mice, reducing metabolic stress caused by physical exertion, due to an increase in NAD+/NADH levels. According to the authors, the activation of energy metabolism in skeletal muscles induced by maqui extract may enhance mitochondrial biogenesis and function, thereby protecting against damage caused by oxidative stress.

Maca is capable of alleviating fatigue and general weakness. Two fractions isolated from maca polysaccharides have been found to reduce fatigue symptoms depending on the concentration, as evidenced by the increased duration of swimming in water and the level of liver glycogen in animals. This was also reported in another study. When using a supplement containing maca extract, fatigue relief was observed in rats during the swimming test. In a swimming exercise that caused ROS formation and oxidative damage in rats, maca polysaccharides removed radicals and not only reduced animal fatigue but also eliminated radicals [58].

Maca has the ability to absorb free radicals and protect cells from oxidative stress [59]. The polysaccharides rhamnose and arabinose in the ethanolic extract exhibited the highest antioxidant activity. Along with reducing fatigue symptoms (increased swimming duration depending on the dose), maca polysaccharides increased SOD activity and reduced MDA content, indicating the suppression of lipid peroxidation activity [60].

More convincing data on the involvement of antioxidant system enzymes is presented in an experiment on aging rats. It has been shown that polysaccharides from maqui can increase the levels of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase) in the muscles of aging rats [61]. The data suggest that polysaccharides, by enhancing the activity of antioxidant enzymes, can reduce oxidative damage mediated by ROS in skeletal muscles.

There is evidence that the essential oil, lipids, and polysaccharides from black maca exhibit higher antioxidant activity than those from yellow or red maca [62].

It has been shown that the anti-radical activity also depends on the phenotypes of the poppy. Thus, when evaluating the methanol, aqueous, and chloroform extracts of the poppy, it was found that the methanol extracts of yellow and grey poppy exhibited moderate anti-radical activity [63].

The immunomodulatory effect of maca has been noted [64]. Immunostimulatory analysis showed that the polysaccharide MC-1 from maca can significantly enhance pinocytic and phagocytic capacity, as well as stimulate the secretion of NO, TNF-α, and IL-6 by RAW 264.7 cells, primarily involving Toll-like receptor 2, complement receptor 3, and mannose receptor. These results suggest that MC-1 could be used as an attractive functional food supplement for individuals with weakened immune systems.

Maca has a low degree of acute oral toxicity in animals and cellular toxicity *in vitro* [65].

Maki polysaccharides can exhibit antitumor activity due to their immunostimulatory ability and lack of toxicity, which is important since this plant is also a food product. It has been demonstrated that the polysaccharide MC-2, consisting of arabinose, mannose, glucose, and galactose in certain ratios, can inhibit tumor growth by suppressing the expression of M1 macrophage-related receptors and the conversion of M2 macrophages to M1 [66]. It turned out that the antitumor activity depends on the molecular weight of the polysaccharide, the degree of branching, and water solubility. In particular, it has been shown that higher molecular weight and water solubility enhance the antitumor effect.

Conclusion

Thus, the main biological activity of all the components of the food supplement is aimed at moderately reducing elevated blood pressure, lowering elevated blood sugar levels, and reducing elevated cholesterol levels. For instance, the extract of Bergamot fruit (a source of flavonoid glycosides bruteridine and melitidine) exhibits a pronounced statin-like effect [67]; the extract of Wild Yam (Dioscorea), containing diosgenin, has a hypolipidemic effect [68]; the extract of Barberry fruit, due to the presence of berberine, has hypolipidemic and hypoglycemic effects, as well as moderate antispasmodic and hypotensive effects [69]; the extract of *Peruvian Maca* has a hypoglycemic effect, promotes increased performance, and has antidepressant effects [70].

For the developed biologically active food supplement, test studies on experimental animals *in vivo* have been conducted, confirming the spectrum of its biological activity (hypoglycemic and hypocholesterolemic effects). In the developed course scheme for humans (20-day intake with a repeated course every 6 months), with normal cholesterol levels and blood glucose concentration, the biologically active food supplement will reduce the risk of developing hyperglycemia and hypercholesterolemia while also moderately lowering these indicators when they exceed the physiological norm.

Additional pharmacological properties of the developed biologically active food supplement: immunomodulatory, oncoprotective, anti-inflammatory, hepatoprotective, antibacterial, antiviral, and fungistatic, as well as fertility enhancement.

Based on the primary and additional activities of the components of the developed biologically active food supplement, it may exhibit a comprehensive preventive effect concerning the aforementioned age-related pathological processes. Current research is aimed at verifying this hypothesis.

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