



## Review

# Goji Berry: Health Promoting Properties

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**Abstract:** Since ancient times, it has been noticed that Goji berry fruit juice, roots and leaves consist of ingredients that contain a wide variety of bioactive substances. The consumption of goji berry fruits results in properties which improve the subjective feeling of general well-being. The aim of this work is to present the information from the existing literature on the possible role of goji berry plant parts and their extracts as a functional food. *Lycium barbarum* Polysaccharides (LBP) and polyphenols are the most researched aspects of fruits associated with the promotion of human health. Goji berry fruits demonstrated anti-oxidative properties that are associated with age-related diseases such as diabetes, atherosclerosis and antitumor and immunoregulatory activities. Bioactive secondary metabolites contained in fruit lead to positive effects for human vision, while other biochemicals contained in the root bark have shown hepatoprotective and inhibitory actions on the rennin/angiotensin system. The results presented so far in the literature verify their use in traditional medicine.

**Keywords:** goji berry; functional foods; antioxidant; health; antibacterial; health promotion



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## 1. Introduction

Modern life-styles and dietary habits are the main cause of several human modern diseases such as diabetes, hepatitis and cardiovascular issues [1–3]. About 1/5 of the known plant species [4] that have participated in pharmaceutical studies cover a wide range of beneficial effects on human health, animal welfare and crop protection by enhancing human health against free radical damage [5–13]. The high concentrations of phytochemicals found in plants are accumulated mainly in their fruits and vegetables. Among beneficial phytochemicals, antioxidant compounds including phenolics, anthocyanins, carotenoids, and tocopherols may be used as a supplement for the human body by acting as natural antioxidants [14]. Thus, the consumption of fruit and vegetables has been linked with several health benefits, as a result of medicinal properties and high nutritional value [15] and is recommended by many scientists throughout the world [16]. In more detail, many studies mention the antioxidant and pharmacological activities of different plant extracts [17–20].

Among important plant species with significant biomedical issues is the Goji berry where fruit juice, roots and leaves contain ingredients that have a variety of bioactive properties [21–24].

The objective of this paper is to provide a review of phytochemical studies that have addressed the beneficial effects for human health of bioactive compounds contained in Goji berries.

## Search Strategy

An electronic literature search was conducted using PubMed, Medline (OvidSP), and Google Scholar for the period between 1992 to 2022. Additional articles were identified from references in the retrieved articles. Search terms included combinations of the following: “goji berry”, “*Lycium barbarum*”, “health promoting effects”, “phytochemical”, “antioxidant”, “*Lycium barbarum* polysaccharides” and “pharmacological”. The search

was restricted to articles in English that addressed the phytochemical constituents and pharmacological properties of goji berries.

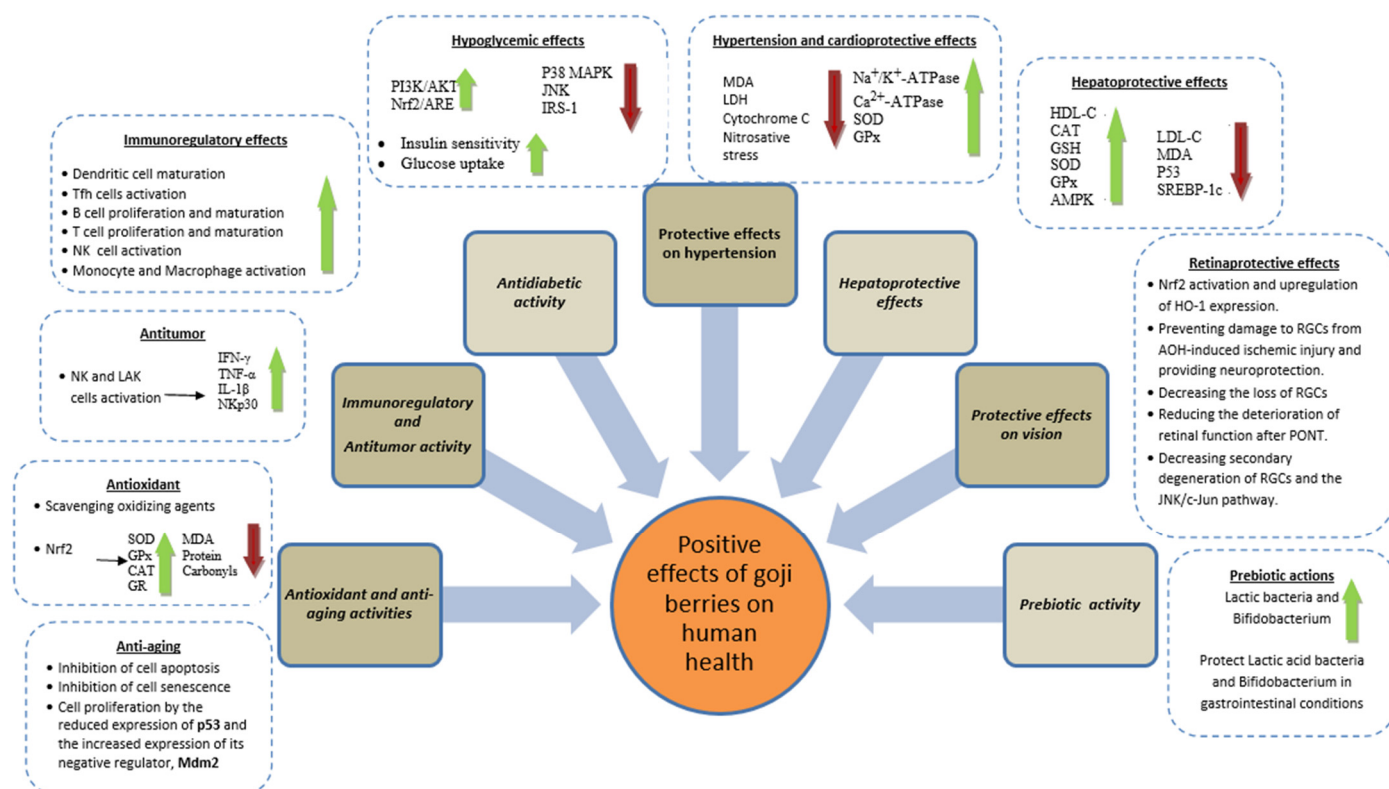
## 2. Bioactivities

### 2.1. Antioxidant Activity

The most studied molecular mechanism of the oxidation of cellular components is that of lipid peroxidation. This is a circular feedback chain process, which, if started and not suspended in time, can oxidize all the biological material. DNA can tolerate a large number of different oxidative lesions, depending on the factors that cause them. Unlike oxidized proteins, which are usually fragmented and their amino acids reused, the oxidized DNA can be repaired in situ. Insufficient DNA repair can result in mutation and, ultimately, cell death by either necrosis or apoptosis.

The amino acids cysteine, methionine, tyrosine, phenylalanine, tryptophan and histidine are more susceptible to oxidative modifications. Relatively recent research results in this field commented on the fact that oxidative modifications of amino acid residues in proteins, besides the negative effects, may also play a positive role by participating in the redox signaling process.

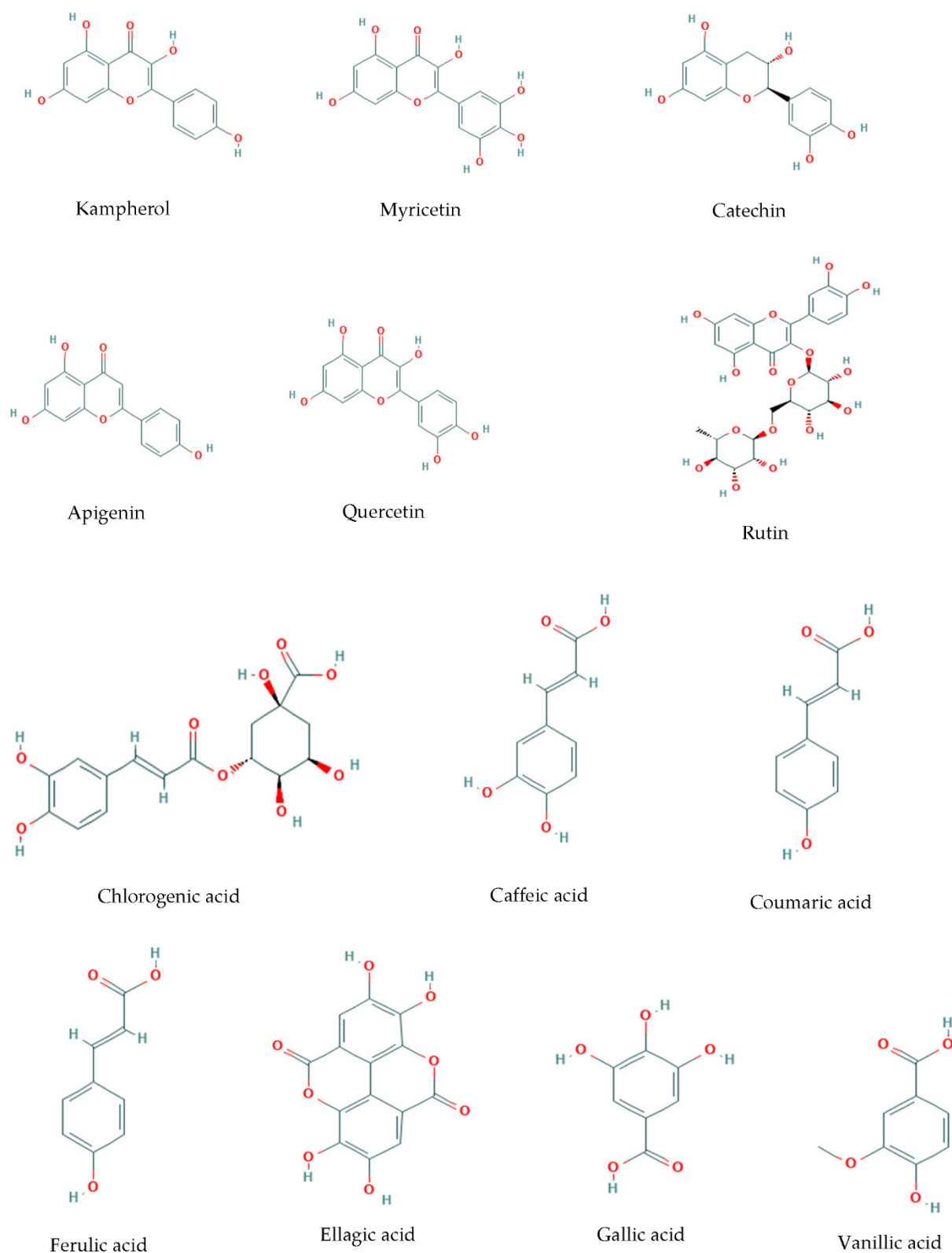
Goji berries have been shown to possess antioxidant properties, neutralizing the oxidative action of free radicals and activating antioxidant mechanisms (Figure 1), such as an increase in superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPx), catalase (CAT), and erythroid-derived 2-like 2 (Nrf2) expression of several antioxidant and cytoprotective enzymes [25]. Thus, *L. barbarum* extracts exhibited the binding of peroxide anion radicals and the subsequent reduction of their activity [26].



**Figure 1.** Health-promoting properties of goji berry fruits and extracts.

The protective effect on the inhibition of lipid peroxidation by goji berry extracts is probably due to the polyphenols of goji berry fruit (Figure 2) [27]. Caffeic acid, which is the main hydroxycinnamic acid in goji berries, not only has potent antioxidant effects but also has anti-inflammatory and anti-cancer effects, while recent studies have shown that caffeic

acid in its free form or conjugated to other groups, such as quinic acid and sugars, has a protective effect against Alzheimer's disease [28].



**Figure 2.** The chemical structure of the polyphenols contained in “Goji berries”.

Moreover, ethanol extract (70% *w/v*) of *L. chinense* protects hepatic cells against oxidative stress-induced cell damage by removing intracellular ROS, SOD recovery, CAT and glutathione action, reducing lipid oxidation, DNA destruction and protein carbonyl values [29]. Further, Changbo et al. [30] have shown that the administration of LBP in mice can reduce the oxidative stress caused after exercise in swimming, increasing the antioxidant enzymes SOD, CAT and GPx.

An important ingredient that contributes to the antioxidant activity of fruits is also AA-2βG, which has similar antioxidant properties to vitamin C. Studies focusing on its effects showed that it exhibits strong binding activity against DPPH and H<sub>2</sub>O<sub>2</sub> and inhibits H<sub>2</sub>O<sub>2</sub>-mediated hemolysis better than vitamin C. Studies have also demonstrated similar effects in the binding of OH radicals. Although the *in vitro* antioxidant capacity has shown that AA-2βG presented lower activity compared to vitamin C; on the contrary, *in vivo* studies demonstrated that AA-2βG protected mice liver from carbon tetrachloride-induced acute liver injury better than vitamin C [31].

Furthermore, several studies have identified the protective mechanisms of the biochemical action of goji berries in relation to the induction of the Nrf2 nuclear factor [25,32]. A recent study, suggested that goji berry aqueous extracts exhibit antimutagenic activity, protecting DNA against peroxy and hydroxyl radicals [33]. In the context of the same study, substantial antioxidant activity of goji berry aqueous extracts in C<sub>2</sub>C<sub>12</sub> muscle cells was also observed, indicated by increased glutathione (GSH) levels up to 189.5% and a decrease of protein carbonyls and lipid peroxidation by 29.1% and 21.8%, respectively [33].

## 2.2. Antiaging Activity

Aging is defined as the accumulation of various deleterious changes in cells and tissues [34], especially for elderly people [35].

Several studies have shown that genetic and environmental factors regulate specific pathways involved in hormone signaling, nutritional signaling and the detection of mitochondrial and ROS signaling and genomic survival. It is a common belief that the accumulation of the effects of oxidative stress contributes to the aging process [36–38]. For this reason, many of the experimental aging models use the pouring of D-galactose into mouse or rat tissues for a period of 6–8 weeks as a toxin in order to produce free radicals [39]. According to Deng et al. [40], the addition on a daily basis of 100 mg LBP/kg to the diet of mice reduced serum advanced glycation end products (AGE), retrieving the memory pointer back to experimental animals, increasing superoxide dismutase levels in erythrocytes and finally helping them to restore kinetic activity.

The life cycle of *Drosophila melanogaster* (fruit-fly) has been used as an alternative model for aging studies. Based on this model, the addition of 16 mg LBP/kg shows a statistically significant increase of the average life span of male insects [41].

Furthermore, studies conducted on elderly mice have shown that the consumption of 200–500 mg/kg of LBP promotes oxidative stress reduction, as it reduces the oxidative stress markers associated with the aging process [42]. It has also been reported that LBP activates the antioxidative pathways Nrf2/ARE and Nrf2/HO-1 by activating antioxidants and detoxifying enzymes. One of these enzymes is heme oxygenase-1 (HO-1), which is regulated by the factor associated with the nuclear factor erythroid 2-related factor 2 (Nrf2) [43].

*In vivo* studies on Factor Nrf2 have shown that it plays an important role in the endogenous antioxidant system by regulating the expression of important antioxidant enzymes, such as oxygenase-1 (HO-1), SOD and CAT. In particular, in oxidative stress or exogenous (pharmacological) activation, Nrf2 moves into the cell nucleus and induces the expression of antioxidant enzymes by blocking the antioxidant response (ARE) [44]. It has also been commented that activation of PI3K/AKT/Nrf2 not only prevents the development of oxidative stress but also prevents metabolic glucose abnormalities such as the occurrence of insulin resistance. Activation of Nrf2 by LBP offers a new alternative

therapeutic approach to the prevention of insulin resistance caused by a long-term high-fat diet [45].

The effect of ultraviolet radiation (UVB) causes skin damage by inducing oxidative and inflammatory lesions and thus causes aging and carcinogenicity of the skin. The protective effect of LBPs through the induction of Nrf2 is likely to exert a protective effect against the negative effect of ultraviolet radiation on the skin by binding to the active radicals and reducing DNA damage, resulting in the suppression of the ultraviolet-induced P38 MAP pathway. Based on the previous beneficial effects, LBP could potentially be used as an ingredient in products intended to protect the skin against oxidative damage from environmental conditions [32].

A recent study investigating retinal protection from damage caused by I/R radiation showed that activation of the Nrf2/HO-1 antioxidant pathway was adapted to neutralize damage to the retina. The use of LBP not only reduced the production of ROS but also enhanced the activation of the Nrf2/HO-1 antioxidant pathway in retinas under the influence of I/R [46].

All of the previous studies support that LBP has positive anti-aging effects, while a clinical study indicates that dietary intake of a total of 500 mg of *L. barbarum* over 10 days can significantly reduce plasma triglyceride levels and increase levels of cyclic adenosine monophosphate (cAMP) and SOD [47].

As the anti-aging effects of *L. barbarum* display a wide range of target tissues, it is believed that it can overall protect cells from oxidative, hyperglycemic and hyperlipidemic conditions. According to the results of a previous clinical study conducted in alloxan-treated rabbits, the LBP group reduced the blood glucose levels [48].

In addition to polysaccharides, the presence of components in fruits, such as carotenes, betaine, polyphenols and vitamin C in the precursor form of 2-O- $\beta$ -D-glucopyranosyl-L-ascorbic acid, contributes to antioxidant and anti-aging properties of the goji berry fruit. Thus, betaine has been shown to have a protective effect against skin aging by ultraviolet radiation by mouse-assisted research. Betaine's protective effect is mediated by inhibition of the extracellular kinase signal transducer (ERP), protein kinase (MEK) and metalloproteinase 9 (MMP-9), resulting in a reduction in collagen wrinkles and damage caused by UVB [49].

Finally, the regulation of the operation of a basic organ, such as the liver or kidneys, results in the regulation of other organs or even of the entire body, according to the traditional Chinese medicine theory. Based on this theory, in traditional Chinese medicine, the use and consumption of *L. barbarum* fruits is recommended for the treatment of aging-related diseases due to the appearance of a wide range of positive effects, reducing all risk factors in aging-related diseases.

### 2.3. Antitumor and Immunoregulatory Activity

The defensive mechanisms of vertebrates are also known as the immune system. The immune system recognizes and destroys foreign invaders and toxic substances by a process known as an immune response. The molecule that causes the immune response is called an antigen. In addition, these mechanisms are involved in the body's effort to remove aged or damaged cells, as well as destroying cancer cells, while sometimes they cause damage against the tissues of the organism itself.

The two main groups of cells in the immune system are the cells of the medullary line and the lymphocytes. Lymphocytes include B-lymphocytes and T-lymphocytes as well as a large granular cell, NK (or natural killer cells). The medullary cells consist of monocytes/macrophages, dendritic cells, neutrophils, eosinophils and basophils. B lymphocytes have an antibody molecule in their membrane, whereas T lymphocytes have an antigen-binding receptor in their membrane. When a B cell encounters an antigen, it quickly divides and differentiates into a B-cell memory and a B-cell effector or plasmid cell. Plasmocytes produce a large number of antibodies (antibody, Ab) or immunoglobulin (immunoglobulin, Ig) that act on the antigen and destroy it. T-lymphocytes, when they meet an antigen or



tumor, secrete cytokines (growth factors), directly killing the infected target cell (CD8 killer T cells) and also activating B-cells to make antibody responses and macrophages to destroy microorganisms that either invaded the macrophage or were ingested by it (CD4 helper T cell). There are two types of immunity—humoral and cellular. Humoral immunity is mediated by antibodies produced by B cells and is the main defensive mechanism against extracellular microbes and their toxins, with secreted antibodies binding to them by inducing their elimination. Cellular immunity is mediated by T cells, with dendritic cells playing an important role against antigens.

A clinical study completed by Cao et al. [50] examined the effect of a combination of lymphokine-activated killer (LAK)/IL-2 and LBP on advanced cancer patients (79 patients). The results of this study showed that the response rate and duration of mean tumor regression of patients treated with LAK/IL-2 plus LBPs was higher than those of patients receiving only LAK/IL-2. LAK/IL-2 plus LBP therapy resulted in a more pronounced increase in NK and LAK activity than LAK/IL-2 alone. Furthermore, a study carried out by Gan et al. [51] showed that the administration of LBP3p polysaccharide enhanced the immune system in S180-bearing mice by increasing spleen lymphocyte proliferation and cytotoxic T-lymphocyte activity (CTL).

However, results published by Zhang et al. [52] showed that LBP therapy inhibited growth of hepatoma cell line QGY7703, phase S, phase interruption and induction of apoptosis, as well as a simultaneous increase in the amount of cellular RNA and  $\text{Ca}^{2+}$  concentration in human tissues.

Clinical studies demonstrated the immunomodulatory effects of standardized *L. barbarum* (GoChi) fruit juice on elderly healthy people in China. The results showed that the GoChi group differed, statistically increasing the number of lymphocytes and levels of interleukin-2 and immunoglobulin G. This study concludes that daily consumption of GoChi significantly increases several immune responses and subjective feelings of general well-being without any undesirable effects [21,22].

Follicular helper CD4 T helper cells (Tfh) are the specialized help providers in B lymphocytes since they are necessary for their maintenance and for differentiation into plasmacytes and memory B cells. For this reason, the correlation of Tfh with the production of antibodies from B lymphocytes was studied. Su et al. [53] investigated whether LBP upregulated expression in such molecules on Tfh cells. BALB/c mice were administered 5 mg/kg, 25 mg/kg and 50 mg/kg LBP daily for 7 days, and the enhancement of the humoral immune response by the activation of Tfh cells using LBP was confirmed by the increase of the expression of numerous molecules, including CXCR5 and PD-1 surface markers. Furthermore, Yang et al. [54] showed in their study that LBPs can enhance the immune system against antigenic infection by enhancing phagocytosis in RAW264.7 phagocytes.

He et al. [55], by observing intracellular ROS production and DNA damage, reported a stimulation effect of LBP on the apoptosis of MCF-7 human breast carcinoma cells and the inhibition of the cell cycle in the G0/G1 phase.

Moreover, Huang et al. [56] investigated the mechanisms of LBP suppressive action against breast cancer in MCF-7 cells in vitro. The results of their study showed that LBP therapy can inhibit the proliferation of MCF-7 cells with insulin-like growth factor 1 (IGF-1) in a dose- and time-dependent manner to suppress phosphatidylinositol 3-kinase activity (PI3 K) and phosphorylated-PI3 K (p-PL3 K) inhibit protein-1 (HIF-1) accumulation caused by hypoxia and suppress the expression of vascular endothelial growth factor (VEGF) mRNA and protein production. These results indicated that LBPs could inhibit tumor cell growth by suppressing IGF-1-induced angiogenesis via the PI3 K/HIF-1/VEGF signaling pathways. In a recent study completed by Deng et al. [57] it was presented that LBP3 polysaccharide could reduce immune toxicity and enhance the antitumor activity of doxorubicin in mice. The results of the aforementioned study showed that LBP3 did not offer protection against body weight loss caused by dox, but it promoted the recovery of body weight starting 5 days after dox treatment in tumor-free mice. Furthermore, LBP3 was found to promote cell cycle recovery in bone marrow cells, improve peripheral blood

lymphocyte counts, and restored the cytotoxicity of natural killer cells. Moreover, the antitumor activity of dox, peripheral blood and lymphocyte counts has been improved.

Apart from polysaccharides, phytochemical compounds mentioned previously contribute to the anti-aging activity exerting a protective effect against cancer cells. For example, betaine has been shown to have an inhibitory effect on colorectal cancer because of its anti-inflammatory action. Kim et al. [58] showed that adding betaine to a mouse diet could achieve a reduction of the incidence of colitis associated with cancer by reducing the levels of ROS and its ratio with oxidized glutathione (GSSG), related to the inflammation of cytokines such as IL-6, IL-1 $\beta$  and IL-22 and protein levels of COX-2 and iNOS with azoxymethane-induced colitis. In addition, Hsu et al. [22] demonstrated that the inhibition of colonic HT29 cancer cells from a mixture of nanoparticle and carotenoid extracts from *L. barbarum* was activated by increasing expression of P53 and P21, reducing the expression of CDK1, CDK2, cyclin A and cyclin B arresting cell cycle at G2/M.

The antitumor activity of goji berry extracts (primarily LBP-based studies) is mainly due to their ability to induce the disruption of cell cycle apoptosis and the inhibition of some important signaling pathways that act as carcinogenic protective agents by eliminating cancerous cells.

#### 2.4. Antidiabetic Activity

The number of patients with diabetes worldwide has quadrupled over the last 30 years, and it is the ninth leading cause of death. One in 11 adults today has type II diabetes, accounting for 90% of diabetes cases, and the prediction is that by 2050, one in three will suffer from diabetes. The majority of people suffering from diabetes are aged between 45 and 64.

Sugar, a common constituent of diet, is also a major factor often responsible for elevating the glucose level in diabetic patients [59]. Diabetes mellitus is a metabolic disease characterized by an increase in blood sugar (hyperglycemia) and a metabolic disorder of glucose (C<sub>6</sub>H<sub>12</sub>O<sub>6</sub>), either as a result of decreased insulin secretion or due to a decrease in the sensitivity of cells to insulin. Insulin is a hormone produced in the pancreas that forces the liver and muscle cells to absorb blood glucose and store it as glycogen for future body energy needs. In case the insulin concentration in the body is low or zero and glucose absorption cannot take place, the body begins to use fat as a source of energy by transporting lipids from adipose tissue to the liver [60]. Nowadays, there are known various types of diabetes. The main diabetes types are type I and type II. In general, diabetes is associated with the risk of serious health complications, including myocardial infarction, stroke, kidney failure, vision loss and premature death. So required care for diabetics is likely to be needed for many years [61].

The effect of the antidiabetic action of goji berry extracts has been investigated in various studies. Goji berries may have a positive effect on blood glucose control, as documented in relevant studies described in a study published by Silva et al. [62]. Furthermore, in a study completed by Wu et al. [63] feeding of type 2 diabetic mice with goji berry extract for 4 weeks showed a decrease in blood glucose levels by 35%. Moreover, Zhang et al. [64] suggested that the fraction LBPF4-OL of the LBP promotes lymphocyte proliferation secreting TNF- $\alpha$  and IL-1 $\beta$ . Luo et al. [48] also showed that *L. barbarum* extracts have hypoglycemic and hypolipidemic effects as well as strong antioxidant activity in rabbits with diabetes and hyperlipidemia from aloxane.

One of the causative factors for insulin resistance development is oxidative stress. Oxidative stress is one of the factors that can activate the JNK pathway under the diabetes condition. Recent research presented that under an oxidative status, the nuclear factor Nrf2 plays a role in insulin-mediated glucose uptake [33]. The positive effects on insulin resistance from Nrf2 activation caused from the enhancement of insulin sensitivity due to the decrease of ROS production are presented in a study completed by Bagul et al. [65]. Nakatani et al. [66] showed also that activation of c-jun N-terminal kinase (JNK) leads to a decrease of insulin sensibility due to the increase of IRS-1 serine phosphorylation

insulin target tissues, while insulin resistance status was improved in the JNK-KO of mice. Furthermore, studies done by Kaneto [67] commented that the activation of p38 mitogen-activated protein kinase (MAPK) and JNK signaling can directly or indirectly promote diabetes. It has been reported that the JNK pathway plays a crucial role in the progression of insulin resistance [68].

Another positive finding regarding the use of LBP was reported by Yang et al. [69]. According to the authors, there is a link between oxidative stress, Nrf2 activity and insulin resistance. According to the above-mentioned study, in vivo and in vitro studies demonstrated that high-fat induced-insulin resistance could be ameliorated by LBP by the upregulation of the PI3K/AKT/Nrf2 signaling pathway. Due to this reaction, it was suggested that LBP may have a promising role in managing insulin resistance-associated oxidative stress in acute or chronic liver damage. Furthermore, Cai et al. [70] studied 67 patients in vivo for three months and found protective effects against the two types of hypoglycemia, lowering the glucose levels in the blood and increasing insulin. Finally, Zhao et al. [71] researched the prophylactic effects of LBP using 25 Japanese male diabetic rabbits induced by Alloxan. Results of this study showed improvement in renal function and inflammation in diabetic rabbits. However, the effect was more effective in preventing disease rather than treating it.

### 2.5. Hypertension and Heart Protective Effects

Hypertension is today one of the major public health problems due to its high incidence, its importance in cardiovascular disease and its correlation with a large number of health problems leading to death. Nearly one in two adults (about 103 million people) suffer from hypertension in the United States only [72]. Hypertension is influenced by factors such as genetics, lack of exercise and dietary intake of sodium, which is one of the most common causes of hypertension. It has been reported that the dietary sodium intake has been correlated with blood pressure, confirming the sensitivity of blood pressure to salt [73].

Regarding LBP's protective positive effects on myocardial I/R damage Shao Ping and Pin-Ting [74] used in their study of Wistar adult male rats. In their study, it was presented that LBPs protected rat hearts from I/R injury via upregulation of heart  $\text{Na}^+/\text{K}^+$ -ATPase and inhibition of cardiomyocyte apoptosis concluding the cardioprotective effect of LBP stems caused by their antioxidant, anti-inflammatory and anti-apoptotic activities.

Prophylactic activity of LBP against cardiotoxic side effects of doxorubicin (DOX), which is a potent antitumor agent, has been also demonstrated in acute DOX-induced cardiotoxicity in rats [75,76] and beagle dogs [77]. Data of previous studies indicated that *L. barbarum* fruits and extracts may exert a potent protective effect on DOX-induced cardiomyocyte damage, mainly via antioxidative and free radical-scavenging pathways. Zhang et al. [78] in their study, related the anti-hypertensive effect of *L. barbarum* to down regulated expression of renal endothelial lncRNAs ONE in a rat model of salt-sensitive hypertension. In conclusion, their study commented that *L. barbarum* treatment can restore blood pressure to normal levels. At the same time, the expression of long noncoding RNA (lncRNA) was found to be reduced by the suppression of the antisense mRNA (sONE). Moreover, the improvement of endothelial nitric oxide synthase (eNOS) levels in the hypertensive model rats treated with *L. barbarum* compared with that receiving a high-salt diet was also observed. In addition, Guo et al. [79], using a meta-analysis of randomized controlled trials, presented that *L. barbarum* treatment significantly reduced fasting glucose concentrations while marginally reducing concentrations of total cholesterol and yielded no benefit in terms of bodyweight and blood pressure.

### 2.6. Hepatoprotective Activity

Alcohol use is the third leading risk factor contributing to the global burden of disease, after high blood pressure and tobacco smoking. According to a WHO report published in September 2018, alcohol causes 3 million annual deaths globally and accounts for 5.3% of



all deaths. Despite the three above mentioned factors affecting liver Demori and Voci [80] commented that modern eating habits involving high-calorie diets that lead to obesity also can cause liver diseases such as hepatic steatosis. Chronic alcohol overdrinking (CAO) typically progresses through the stages of fatty liver or simple steatosis, alcoholic hepatitis and chronic hepatitis with hepatic fibrosis or cirrhosis [81].

The use of *L. barbarum* was originally proposed in traditional Chinese medicine for the treatment of liver diseases. Nowadays, studies done by Xiao et al. [82] have proved that feeding alcohol-induced liver injury rats with 300 mg/kg LBP for 30 days showed positive reverse effects, reducing liver injury, preventing the progression of alcohol-induced fatty liver and improving antioxidant function, in contrast with the ethanol group.

Pretreatment with 50 µg/mL LBP of rat normal hepatocyte line BRL-3A cells has shown a significant reduction of 24-hour ethanol-induced over expression of thioredoxin-interacting protein (TXNIP) increasing cellular apoptosis. Xiao et al. [83] also observed an activation of NOD-like receptor 3 (NLRP3) inflammasome and reduction of the antioxidant enzyme expression and ROS. Non-alcoholic fatty liver disease is an important factor in causing hepatocarcinoma and is associated with obesity, insulin resistance and metabolic syndrome. As mentioned previously, obesity leads to a decrease in insulin sensitivity (IR), a decrease in the antioxidant enzymes SOD, CAT and GSH-Px but also an increase in ROS, leading to liver dysfunction, hepatic steatosis and depletion of the hepatocyte population [80,84,85].

Cui et al. [27] examined the effects of *L. barbarum* aqueous (LBAE) and ethanol (LBEE) extracts on oxidative stress and antioxidant enzymes in the liver of rats fed with a high-fat diet (HFD). They concluded that LBAE and especially LBEE have strong antioxidant activities and can prevent or reduce the effects of HFD on several parameters of toxicity in HF rats. LBEE displayed stronger antioxidant and hepatoprotective effects than the aqueous extract of *L. barbarum*, a fact that probably has to do with the higher concentration of polyphenolic content that led to higher antioxidant activity and lipid peroxidation inhibition.

Protection against hepatotoxic effects of CCl<sub>4</sub> has been documented by Kim et al. [86] using two cerebrosides isolated from *L. chinense* fruits (1-O-β-D-glucopyranosyl- (2S, 3R, 4E, 8Z)-2-N-palmitoyloctadecasphinga-4,8-dienine and 1-D-glucopyranosyl-(2S, 3R, 4E, 8Z)-2-N-(2'-hydroxypalmitoyl) octadecasphinga-4,8-dienine) in the culture of rat hepatocytes. Xiao et al. [87] also tested the effects of LBP on oxidative stress and liver necrosis of mice. Both studies showed significant sub-protective action, while in the second, it was shown that LBP reduced hepatic necrosis and alanine aminotransferase (ALT) levels in serum caused by CCl<sub>4</sub>, indicating that the beneficial effect on hepatotoxicity ought partly to reduce the activity of the kappa-B nuclear factor. Additionally, the use of LBP reduced hepatic inflammation by reducing pro-inflammatory mediators and chemokines.

### 2.7. Eye and Vision Activity

Zeaxanthin and lutein are two common carotenoids found in plants and are constituents of the yellow macular pigment in human retina [88]. Biological functions of these macular pigments include the absorption of spectra. The function of these pigments is to absorb the blue light that can cause harm to the retina, but this chronic process of absorption may affect these macular pigments [89].

Glaucoma is the second most common cause of blindness and is a degenerative disease of retinal ganglion cells (RGCs) and the optic nerve and is expected to affect about 111.8 million people between 40 and 80 years by 2040 [90]. The most common types of glaucoma are primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG) [91]. The appearance of glaucoma caused mainly by the progressive disruption of RGC axonal transport or with retinal ischemia. Pathologically, glaucoma is characterized by the death of RGCs and increased intraocular pressure (IOP) [92]. Increased IOP is an important contributor to POAG. Elevation of IOP could cause many changes that are involved in the pathogenesis of glaucoma, such as oxidative stress, glutamate toxicity and ischemia [91].

The positive effects of goji berries on eye diseases such as glaucoma, cataract and rhinitis pigmentosa (RP) have been proposed by Chinese herbalists due to their high concentration of zeaxanthin and their esters, which are readily absorbed into serum, resulting in protection of the retina against free radicals and blue light damage. Leung et al. [93] reported that the levels of these two carotenoids in the serum and tissues of rhesus monkeys after feeding with *L. barbarum* fruits were significantly higher against the control group. Furthermore, clinical studies focused on *L. barbarum* as a therapy for retinal diseases in humans exist in the scientific literature. Chan et al. [94], in a study involving retinitis pigmentosa patients, showed that *L. barbarum* treatment can provide a neuroprotective effect for the retina and could help delay or minimize cone degeneration in RP. The positive effect of goji berries on glaucoma is due to the activation of the microglia at a moderate level resulting in RGCs protection against IOP regulating important intracellular pathways that stimulate the body's defense under stress situations.

Chu et al. [95] studied the positive effects of LBP on preserving retinal function by multifocal electroretinogram (mfERG) analysis of 30 eyes of 30 Sprague-Dawley rats using a partial optic nerve transection (PONT) model in order to study secondary degeneration of retinal ganglion cells. The experimental results demonstrated that the feeding for 4 weeks with LBP, altered the functional reduction caused by PONT by regulating the signal from the outer retina. Li et al. [96] also suggested that LBP can reduce the loss of axons in the central optic nerves (ONs). Preservation of the g-ratio (axon diameter/fiber diameter) in the ventral ONs activates the microglia/macrophages in the ONs 12 h after PONT and finally decreases the magnitude response of microglia/macrophages 4 weeks after PONT. When the supply of blood to the retina is inadequate, the appearance of retinal ischemia due to lack of oxygen results in an altered metabolic function that eventually leads to irreversible cell death. An LBP diet of mice with acute ocular hypertension showed that it reduces the loss of RGC, protecting nerve fiber density, reducing immunoglobulin leakage and increasing blood vessel density [97–99]. Furthermore, similar studies in rats completed by He et al. [100] and Chu et al. [95] confirmed the protection of RGCs, commenting on the importance of Nrf2 activation that leads to an increase of heme oxygenase-1 (HO-1) expression. Thus, the induction of the antioxidant pathway plays an important role in maintaining the redox status of the retina.

The blood-retinal barrier (BRB) is a protective barrier that consists of the outer and inner BRB. The role of the BRB is to maintain the homeostatic condition of the retinal microenvironment and prevent harmful substances from getting into the retina. It has been presented that mice administered with LBP a week before retinal ischemia showed protection against neuronal cell death and to retinal oxidative stress by inhibition of lipid peroxidation and against disruption of the BRB 48 h after reperfusion [99].

Age-related macular degeneration may occur gradually over a period of years (dry AMD) or suddenly in weeks or months (wet AMD). The macula has a large number of light detection cells that provide acute central vision. It is located at the back of the eye and is the most sensitive part of the retina. These cells convert light into electrical signals, sending them through the optic nerve to the brain, where they are “translated” into the images we see. Any damage to the macula leads to a blurred, distorted or dark representation of the center of the field of vision [101]. Studies by Bucheli et al. [102] in elderly people have shown that daily goji berry consumption for a period of 90 days increases plasma zeaxanthin and antioxidant levels. In addition, it protects against hypopigmentation and soft drusen accumulation in the macula of elderly people. The deposition of extracellular amyloid beta ( $A\beta$ ), oxidative stress, and inflammation have all been implicated in AMD. Yoshida et al. [103] has commented that retinal ganglion cells and retinal pigment epithelium also synthesize  $A\beta$ , which are secreted in the posterior eye. Age-related changes in the composition of  $A\beta$  as well as its degradative enzymes lead to an increase in the amount of deposition in the retina [104]. The protective effect of LBPs on macular neurons during the pathogenesis of AMD is due to the protection of these cell neurons from the stress caused by  $A\beta$  [97,98,105].

Finally, Chien et al. [106] examined goji berry effects on dry eye disease in a male Sprague-Dawley rat model. Their study indicated that in the group treated with goji berries, the severity of the kerato conjunctival staining decreased significantly and ameliorated dry eye disease symptoms appeared in a dose-dependent manner.

According to the above-mentioned studies it is believed that Goji berry consumption positively affects eye and vision activity in many ways.

## 2.8. Pre-Biotic Activity

The term probiotic originates from the Greek words pre + bios and has been used with many different meanings in recent decades. Initially, the term “probiotic” was used to describe compounds produced by a protozoan that stimulated the growth of another [107]. Finally, experts from the Food and Agriculture Organization/World Health Organization have identified probiotics as “living microorganisms, which when consumed in sufficient quantities as part of the feed contribute to the beneficial effect of the host” [108].

The use of probiotics extends back to a time before the discovery of microbes. Fermented dairy products were depicted in Egyptian hieroglyphics, and buffalo milk fermentation was traditionally used by Mongolian nomads to preserve their milk during their long journeys [109]. So far, many microorganisms such as fungi, yeasts, bacteria or their mixed combination have been considered or used as probiotics. The two main bacterial genera mainly referred to as probiotics are those of *Lactobacillus* and *Bifidobacterium* [110].

Historically, during the 1800s, the positive effect on human health of the consumption of fermented dairy products was observed by scientists. Although Louis Pasteur identified bacteria and yeasts that were responsible for the fermentation process did not associate these microbes with any apparent health effects. In 1905, Elie Metchnikoff, who had worked with Pasteur in the 1860s, observed that Bulgarian shepherd’s longevity was mainly due to the lactobacilli used for yogurt fermentation and the presence of these lactobacilli in the sheep intestine in Bulgaria not with the yogurt they consumed but with [111]. In particular, Metchnikoff, in his study, “The Prologue of Life” in 1908, assumed that lactic acid bacteria detected in Bulgarian yogurts, the so-called Balkan Bulgarian, later known as *Lactobacillus bulgaricus* (now called *L. delbrueckii* subsp. *bulgaricus*) and *Streptococcus thermophilus*, are responsible for enhancing the intestinal system by inhibiting microbial fermentation, resulting in a reduction in unwanted by-products, such as amines and ammonia. Thus, for the first time, Metchnikoff highlighted the importance of specific micro-organisms and their contribution to human health and longevity.

Prebiotics are components of non-digestible foods that effectively affect the host by favoring growth and/or bacterial activity in the large intestine [112,113].

The term “symbiotic” is defined as a mixture of probiotics and prebiotics that beneficially affect the host by improving the survival of the beneficial microflora, enriching it with live beneficial bacteria found in dietary supplements in the gastrointestinal tract. These microorganisms promote health and thus improve welfare in the gastrointestinal tract. Symbiotics are aimed at enhancing the survival and activity of probiotics as proven in vivo, as well as stimulating *Bifidobacterium* species [111].

The prebiotic action of goji berries has been shown by its addition to yogurt [114], which resulted in maintenance the viability of lactic acid bacteria (LAB) at probiotic levels (106–107 log CFU/mL) during 21 days of storage compared to classic yogurt control. Similar results were presented in the study of Baba et al. [115], where the addition of aqueous extracts of *L. barbarum* to yogurt significantly improved the bioavailability of probiotic bacteria *Lactobacillus* spp. and *Streptococcus thermophilus*.

Furthermore, Liao et al. [116] demonstrated the beneficial prebiotic effect of the addition of *L. barbarum* to fermentation in Sichuan pickle (traditional Chinese pickle). According to the results presented in this study, *L. barbarum* addition not only increased the amount of LAB but also improved considerably the organoleptic quality and reduced the nitrite content of the pickle. Additionally, the results of a recent study completed by Zhou et al. [117] demonstrated that LBP improved the tolerance of *B. longum* subsp. *infantis* Bi-26 and

*L. acidophilus* NCFM to the gastrointestinal environment. These results were also found to be in line with the study completed by Skenderidis et al. [19] that indices that LBP promotes the proliferation protecting *Bifidobacterium* and *Lactobacillus* strains by enhancing carbon and energy metabolism. These results also reported that the viability of *L. casei* was less affected, followed by *B. lactis* Bb12, which showed the greatest tolerance in the acidic environment, while the survival of *B. longum* 42 was low. Similar results were also confirmed by González-Rodríguez et al. [118], where *B. longum* 42 showed lower resistance in low pH conditions compared to *B. lactis* Bb12.

To confer a health benefit on the host, the LAB must be able to overcome the physical and chemical barriers of the gastrointestinal tract, especially acidic and proteolytic enzymes and bile stresses [119]. Consequently, the LAB should be resistant to the gastrointestinal environment.

The existence of an extracellular polysaccharide film produced by certain lactic bacteria or *Bifidobacterium* has also been reported in the literature [120,121]. This polysaccharide film protects probiotic bacterial cells from the environment and acts as a shield against the conditions prevailing in the gastrointestinal tract and helps them to survive. It has also been reported that *Bifidobacterium longum* strains produce larger amounts of this film than Bb12, resulting in higher bile strength [19]. This resistance is related to the binding of bile salts from the polysaccharide film, resulting in a reduction in its antimicrobial activity [116,120]. Finally, Skenderidis et al. [19] confirmed the increase of the Bb12 strain viability induced by goji berry extracts. This increase is probably related to goji berry polysaccharides, which consist of galactose, glucose, fructose, arabinose, mannose and xylose molecules, which are also the structural molecules of this extracellular polysaccharide antimicrobial [120–123].

### 2.9. Other Bioactivities

Additional bioactive effects of goji berries, such as skin protection and its synergistic potential within fertility treatment by inducing spermatogenesis, have been reported [25,33,124–126]. Studies carried out with phenolic compounds isolated from the fruits of *L. barbarum* showed that the extracts had a bactericidal effect against Gram positive and Gram-negative bacteria [10]. On the other hand, *L. chinense* leaf extracts were found to be more potent as antimicrobial agents than the fruit extracts, with the best microbiocidal activity exerted on *Bacillus subtilis* [127].

## 3. Conclusions

There are many scientific research results that support the positive effects of the consumption of goji berry fruits and their plant parts (bark, leaves) extracts. Their potential health benefits include protection against oxidative damage, antidiabetic, immunoregulatory, vision protective, hepatoprotective, and prebiotic activities that are associated with the promotion of risk reduction in the development of chronic diseases such as cancer, diabetes, cardiovascular disease, Alzheimer's disease, cataracts, and age-related diseases. Therefore, the screening of individual constituents of bioactive goji berries that exhibit health-promoting properties requires further investigation. This is because a cause–effect relationship between the intake of goji berries and its health effects can only be established when the composition of goji berries is properly characterized and standardized. Furthermore, extensive investigation is needed to examine the effects of adding these beneficial bioactive phytochemicals from goji berries, using advanced technologies, into food systems. Further research is also needed to evaluate the effectiveness of goji berry extracts in the food ecosystem and to establish their role as a functional agent in the design of new fortified foods.

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