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REVIEW ARTICLE

Supercharging metabolic health with *Lycium barbarum* L.: A review of the therapeutic potential of this functional food for managing metabolic syndrome

Javad Sharifi-Rad[1] | Maria Magdalena Quetglas-Llabrés[2] | Antoni Sureda[2,3] | Lorena Mardones[4] | Marcelo Villagran[4,5] | Eda Sönmez Gürer[6] | Jelena Živković[7] | Shahira M. Ezzat[8,9] | Ahmed Zayed[10] | Safa Gümüşok[11] | Ceyda Sibel Kılıç[11] | Babatunde Fasipe[12] | Ismail Laher[13] | Miquel Martorell[14]

[1]Facultad de Medicina, Universidad del Azuay, Cuenca, Ecuador

[2]Research Group in Community Nutrition and Oxidative Stress and Health Research Institute of Balearic Islands (IdISBa), University of the Balearic Islands-IUNICS, Palma de Mallorca, Mallorca, Spain

[3]CIBEROBN (Physiopathology of Obesity and Nutrition), Instituto de Salud Carlos III, Madrid, Spain

[4]Department of Basic Science, Faculty of Medicine, Universidad Católica de la Santísima Concepcion, Concepción, Chile

[5]Scientific-Technological Center for the Sustainable Development of the Coastline, Universidad Católica de la Santísima Concepción, Concepción, Chile

[6]Faculty of Pharmacy, Department of Pharmacognosy, Sivas Cumhuriyet University, Sivas, Turkey

[7]Institute for Medicinal Plant Research "Dr Josif Pančić", Tadeuša Košćuška 1, Belgrade, Serbia

[8]Department of Pharmacognosy, Faculty of Pharmacy, Cairo University, Cairo, Egypt

[9]Department of Pharmacognosy, Faculty of Pharmacy, October University for Modern Science and Arts (MSA), 6th of October, Egypt

[10]Department of Pharmacognosy, Tanta University, College of Pharmacy, Tanta, Egypt

[11]Department of Pharmaceutical Botany, Ankara University Faculty of Pharmacy, Ankara, Turkey

[12]Faculty of Basic Medical Sciences, Department of Pharmacology and Therapeutics, Bowen University, Iwo, Nigeria

[13]Faculty of Medicine, Department of Anesthesiology, Pharmacology and Therapeutics, The University of British Columbia, Vancouver, British Columbia, Canada

[14]Department of Nutrition and Dietetics, Faculty of Pharmacy, and Centre for Healthy Living, University of Concepción, Concepción, Chile

Correspondence
Javad Sharifi-Rad, Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Email: javad.sharifirad@gmail.com

Miquel Martorell, Department of Nutrition and Dietetics, Faculty of Pharmacy, and Centre for Healthy Living, University of Concepción, Concepción, Chile.
Email: mmartorell@udec.cl

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Abstract

Metabolic syndrome (MetS) is a common disorder involving a cluster of metabolic abnormalities, such as abdominal obesity, hypertension, dyslipidemia, insulin resistance, and atherogenic profile. MetS is characterized by an increase in oxidative stress and a chronic proinflammatory state, which are directly related to the development and progression of this pathology. It has been seen how a healthy lifestyle and good dietary practices are key to improving the different metabolic parameters and, therefore, play a fundamental role in reducing the risk of developing diabetes. The present review focuses on the research evidence related to the therapeutic properties of *Lycium barbarum* L. in MetS gathered in the last years. Several preclinical studies

suggest that *L. barbarum* extracts are a good dietary supplement for the prevention of cardiovascular diseases in people with MetS. This compound has been used for years in traditional Chinese medicine for the treatment of atrophic gastritis, problems related to the lungs, kidneys, and liver, and as a supplement for eye health. In addition, different in vitro and in vivo studies have been carried out that support the properties attributed to metabolites derived from *L. barbarum*, such as polysaccharides that have been shown diverse biological activities. In conclusion, *L. barbarum* extracts have multiple benefits to increase general well-being and immune function. However, there are a limited number of studies related to effect of *L. barbarum* in MetS, but they demonstrated effectiveness in the treatment of obesity, diabetes mellitus type 2, and prevention of diabetes mellitus type 2 complication.

KEYWORDS
goji, immune system, *Lycium barbarum*, metabolic syndrome, oxidative stress, polysaccharides

1 | INTRODUCTION

Metabolic syndrome (MetS) is a common disorder directly related to the increase in the prevalence of obesity and to increased cardiovascular rick (Eckel et al., 2005). MetS is the reflection of a sedentary lifestyle and overnutrition that gives rise to excess adiposity and other comorbidities, including a proinflammatory and prothrombotic state, nonalcoholic fatty liver disease, reproductive disorders (Cornier et al., 2008), cholesterol gallstone disease (Wang et al., 2020), and sleep apnea (Kassi et al., 2011). Moreover, it is part of the group of noncommunicable diseases that have become the main cause of morbidity and mortality in developed and underdeveloped countries (Saklayen, 2018). The main therapeutic approach consists of a change in lifestyle, diet, and physical activity, in addition to a pharmacological intervention for the treatment of alterations, such as hypertension, hyperglycemia, and atherogenic dyslipidemia (Samson & Garber, 2014). Specifically, it has been reported that a reduction in caloric intake and in sodium, saturated fat, cholesterol, and simple sugar intake can help in the clinical management of MetS comorbidities (Di Daniele et al., 2021).

Lycium barbarum L. berry, known as wolfberry or goji berry, is a fruit widely used in Chinese medicine as a bioactive food due to its wide potential health benefits. Various components have been identified, such as carotenoids, fatty acids, fibers, flavonoids, glycerogalactolipids, organic acids, phenolic acids (chlorogenic, caffeic acid, *p*-coumaric acids, quercetin, and kaempferol), polysaccharides, sugars (fructose, glucose, and sucrose), terpenoids, minerals, and vitamins, which are responsible for the beneficial effects of this berry (Masciet al., 2018; Mocan et al., 2019; Spano et al., 2021; Tian et al., 2019; Zou et al., 2010). In addition, *L. barbarum* polysaccharides are macromolecular water-soluble glycoconjugates extracted from goji berry with antioxidant, anticancer, antidiabetic, antiaging, neuroprotective, immunomodulatory, and cytoprotective properties (Tian et al., 2019; Zhao, Jing et al., 2023). A ciabatta bread enriched with goji fresh flesh puree showed the ability to protect against lipid peroxidation and inhibitory activities against key enzymes of MetS (α-amylase and α-glucosidase) (Sicari et al., 2023). It has been also observed that in patients with MetS a supplementation with *L. barbarum* berries, resulted in an increase in serum antioxidant capacity and reduced glutathione (GSH) and a decrease in low-density lipoproteins cholesterol (LDLc), waist circumference, and lipid peroxidation (de Souza Zanchet et al., 2017).

The present review focuses on the research evidence related to the therapeutic properties of *L. barbarum* in MetS. *L. barbarum* has antioxidative, anti-inflammatory, and metabolic regulatory effects, potentially influencing MetS. By meticulously analyzing and synthesizing the existing literature, this study aims to provide profound insights that can guide future research avenues, clinical applications, and interventions for effectively managing MetS and its associated health conditions. The originality and novelty of this work is to bridge historical wisdom with modern science, exploring existing knowledge about *L. barbarum*. It focuses on its potential to address MetS, highlighting positive effects such as improved antioxidant capacity and cholesterol reduction. Supported by experimental evidence, the review aligns with the current trend of researching natural remedies, making it a valuable and innovative contribution to understanding the therapeutic potential of *L. barbarum*.

2 | PATHOPHYSIOLOGY AND THERAPEUTIC APPROACH OF METS: AN UPDATED OVERVIEW

Visceral adiposity has proven to be the main trigger for most of the pathways related to MetS, emphasizing that a high caloric intake is the main causative factor (Rochlani et al., 2017). There are several hypothesized mechanisms for the underlying pathophysiology of MetS, including insulin resistance with fatty acid flux (McCracken et al., 2018), low-grade chronic inflammation, oxidative stress, and neurohormonal activation (Rochlani et al., 2017).

The potential of the adipose tissue to expand and store the excess of energy substrates plays a critical role in the pathophysiology of MetS (Aguilar-Salinas & Viveros-Ruiz, 2019). Chronic energy disbalance provokes adipocyte hypertrophy, endoplasmic reticulum stress, and mitochondrial dysfunction, resulting in systemic release of free fatty acids and lipotoxicity (Denisenko et al., 2020). In this situation, some metabolic pathways, such as de novo lipogenesis, beta oxidation, pyruvate utilization, and serine and GSH synthesis, can be activated in order to manage the excessive flux of energy precursors detected in MetS and to counteract the increase of reactive species. All together evidences that free fatty acids possess significant functions in the link between obesity and insulin resistance. Consequently, insulin resistance induces a proinflammatory environment leading to microvascular damage, endothelial dysfunction, vascular resistance, and hypertension (Sears & Perry, 2015; Zafar, 2020).

The first therapeutic approach for metabolic diseases is mainly focussed on the modification of lifestyle habits (including weight loss and healthy diet and increased physical activity) (Lee et al., 2020). Nonetheless, these lifestyle modifications are often insufficient to normalize risk factors in these patients, and treatment requires additional therapy (Dalle Grave et al., 2013). As MetS represents a cluster of harmful abnormalities, multidrug treatment of single conditions including type 2 diabetes, hypertension, and dyslipidemia, as well as the related comorbidities is needed (Fahed et al., 2022; Lillich et al., 2020). For example, drugs used to reduce insulin resistance are promising, but clinical trials to prove the reduction of cardiovascular diseases are lacking (Grundy et al., 2004). This puzzled treatment with several drugs results in drug–drug interactions, side effects and, insufficient patient adherence, bringing to poor management of the disease (Grundy, 2006; Mendrick et al., 2018).

3 | METS: ARE OXIDATIVE STRESS AND INFLAMMATION REAL TRIGGERS?

3.1 | MetS and oxidative stress

Oxidative stress results from the imbalance between oxidants and antioxidants (Francisqueti et al., 2017), and it is known to be increased in patients with MetS (Esposito et al., 2006). In fact, patients suffering from this disorder have lower antioxidant enzyme activities in plasma and higher amounts of markers for oxidative stress (Monserrat-Mesquida et al., 2020; Sabir et al., 2016). In a review by Rasaee et al. (2021), lower risk for MetS was stated to be related to higher dietary total antioxidant capacity.

Abdominal adiposity is also a key factor contributing to oxidative stress. The increased fat mass together with insufficient irrigation might result in a lack of oxygen and in the induction of cell necrosis. These necrotic cells are tried to be discarded via phagocytosis but, during the process, reactive species such as nitric oxide and hydrogen peroxide are released, also promoting oxidative stress (Francisqueti et al., 2017).

Oxidative stress is found to be a major contributor for the micro- and macro-vascular complications characteristic of MetS (Hutcheson & Rocic, 2012). The pathophysiological changes occurring in mitochondria functioning during MetS are known to be associated with increased production of oxidants and decreased antioxidant defenses (Verda Bitirim et al., 2021). The excess of nutrients in adipocytes leads to compensatory increases in mitochondrial fatty acid oxidation leading to an increase of electron supply to the electron transport chain of mitochondria (Prasun, 2020). Some of these electrons spill off the chain generating reactive oxygen species (ROS). In addition, the excessive accumulation of free fatty acid in adipocytes causes the activation of NADPH oxidase enzyme and the overproduction of ROS (Furukawa et al., 2004).

3.2 | MetS and inflammation

Inflammation is a protective physiological response designed to prevent cellular damage caused by mechanical trauma, microorganisms, or toxins. Inflammation is an acute, self-limited process that must resolve over a period of time. If the inflammation is not resolved adequately, it can become chronic and progress into a pathological process. In chronic inflammation, there is a sustained increase in proinflammatory cytokines and immune cells are in a more activated state, which can lead to tissue damage (Koptagel et al., 2021).

It is well established that MetS is a proinflammatory state in which inflammation-related mechanisms may contribute to insulin resistance. On the other hand, insulin resistance can also alter the anti-inflammatory effect of insulin and, thus, promote inflammation itself (Dandona et al., 2006). When insulin homeostasis is lost and insulin resistance develops, especially in obese people, this state also contributes to MetS (Darroudi et al., 2019). C-reactive protein (CRP), as a biomarker of inflammation, was also evidenced to be elevated in patients with MetS but also in oxidative stress situation (Devaraj et al., 2009; Hutcheson & Rocic, 2012).

Inflammation in adipose tissue occurs when adipocyte storage capacity is exceeded, followed by hypertrophy. Hypertrophy results in the release of adipokines in higher amounts, mainly proinflammatory cytokines (e.g., interleukin (IL)-1, IL-6, tumor necrosis factor α (TNF-α)), and proinflammatory adipokines (leptin and chemerin) circulation contributing to overall inflammation (Elks & Francis, 2010). When central adipose tissue is inflamed, it results in excessive adipokine production, which is released into circulation, contributing to overall inflammation (Elks & Francis, 2010). Eventually, low-grade chronic inflammation is initiated in adipose tissues, spreading to other organs via circulation (Francisqueti et al., 2017; Reddy et al., 2019).

4 | *Lycium barbarum* HEALTH-PROMOTING POTENTIALITIES: FROM PAST TO PRESENT

4.1 | Folk medicinal applications of *Lycium barbarum*–derived remedies

L. barbarum berries have a long history of traditional use in Chinese folk/herbal medicines, since there are reports going back more than

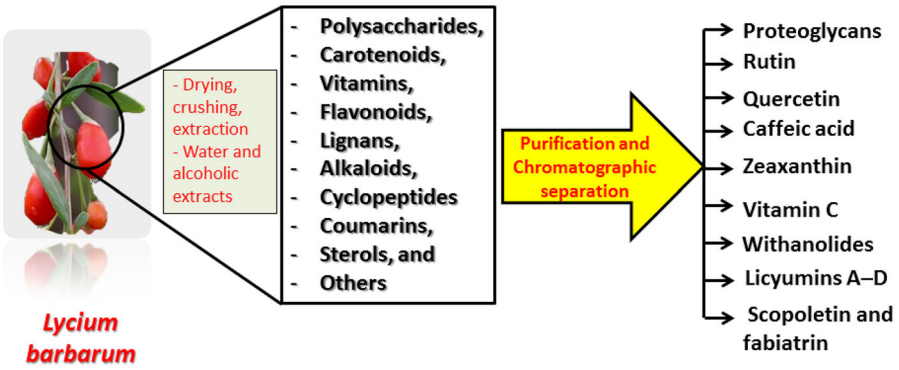

FIGURE 1 *Lycium barbarum* L. provides a wide spectrum of phytochemical classes derived from different organs, which result in numerous bioactive compounds following chromatographic separation and structure elucidation.

1000 years (Tang Dynasty period, 618–907 AD), forming part of the Pharmacopoeia of the People's Republic of China (Gao et al., 2017). In the last decades, *L. barbarum* has become progressively more consumed in Europe and North America (Lei et al., 2022). The plant berries have been traditionally prescribed by herbal healers in different preparations, that is, soups and herbal teas, due to its hypoglycemic and hypolipidemic, directly related to MetS features but also to manage a wide range of health problems related to the liver, eyes, kidneys, and lungs (Cheng et al., 2015; Kulczyński & Gramza-Michałowska, 2016; Ma, Zhang, Teh et al., 2019; Song et al., 2014). Over the last few years, *L. barbarum* berries products have been marketed globally efficiently to be used safely also in Western communities (Potterat, 2010).

4.2 | From *Lycium barbarum* extracts to biologically-active molecules

L. barbarum berries are rich in polysaccharides representing 5%–8% w/w dried fruit, vitamin C, and carotenoids (0.03%–0.5% of dry fruit), that is, mainly zeaxanthin and β-carotene (Masci et al., 2018; Sangiovanni et al., 2017; Spano et al., 2021). Monomeric composition investigation of polysaccharides purchased from Hong Kong Institute of Biotechnology (Shatin, Hong Kong) revealed that they are composed mainly of arabinose (35%), galactose (16%), rhamnose (10%), in addition to small portions of glucose, xylose, and mannose (Xiao et al., 2012). Among the different bioactive compounds present in berries, organic acids, phenolic acids, flavonoids, and oxylipins stand out (Mocan et al., 2018).

In addition, phenolic compounds, including flavonoids, have been reported as the major functional components mostly isolated in the leaves. Examples include rutin, quercetin, isoquercitrin, chlorogenic acid and related derivatives, *p*-coumaric acid, luteolin, kaempferol, and caffeic acid (Conidi et al., 2020; Dong et al., 2009; Zhao et al., 2019). Moreover, the root bark has been reported for other phytochemical classes, that is, alkaloids, lignans, cyclopeptides, anthraquinones, coumarins, terpenoids, sterols, and others (Yang et al., 2017). Figure 1 summarizes phytochemical classes and isolated high-valued bioactive compounds from *L. barbarum* various extracts. Recently, Lei et al. (2022) and Ma et al. (2022) reviewed phytochemicals and bioactivities of *L. barbarum* leaves.

Based on the classes of phytoconstituents mentioned above, various postharvest processes can be carried out, including extraction and chromatographic techniques. For instance, conventional aqueous extraction (temperature: 40–90°C and pH: 2–12 for 30 min) was found to be the optimum for isolation of phenolic compound from *L. barbarum* leaves (Conidi et al., 2020). Moreover, extraction and structural characterization of *L. barbarum* derived polysaccharides were comprehensively reviewed (Tian et al., 2019). Previous reports showed that hot water extraction (70–100°C for 20 min–2 h) is the most commonly used procedure for polysaccharides (Masci et al., 2018; Zhou et al., 2020). Masci et al. (2018) optimized the hot water (5.5 h at 100°C) extraction for five cycles after removal of lipids with refluxing in $CHCl_3$/methanol (2:1). The precipitate was washed with ethanol and acetone and dried. This method resulted in a yield of 23.13% (Masci et al., 2018). It is noteworthy to mention that polysaccharides can be fractionated through precipitation by different volumes of ethanol (Zhao et al., 2016). In addition, modern extraction methods, including microwave-assisted extraction, ultrasonic-assisted extraction, and pressurized liquid extraction, were reported for polysaccharides isolation (Hao et al., 2020).

Moreover, carotenoids can be extracted from the *L. barbarum* berries using hexane/acetone/ethanol (2:1:1, *v/v/v*; with 0.1% butylated hydroxytoluene) assisted by ultrasonic treatment for 30 min (Liu et al., 2014). However, hydroalcoholic mixture of ethanol/water (70:30) and water acidified with 0.5% acetic acid was reported for extraction of phenolic constituents (Mocan et al., 2019).

4.3 | Biologically active molecules and its modes of action

With the recent advances in molecular pharmacology, numerous bioactivities of *L. barbarum*-derived metabolites have been investigated revealing the most likely involved mechanisms. These activities and molecular mechanisms were mainly supported by in vitro and animal models (Cheng et al., 2015). For instance, derived polysaccharides

have been pharmacologically investigated showing neuroprotective, antitumor, immunomodulatory, and antioxidant, among others (Jin et al., 2013; Tian et al., 2019). Table 1 summarizes a number of reported bioactivities for metabolites isolated from *L. barbarum* with the underlined mechanism of action.

5 | HYPOGLYCEMIC AND HYPOLIPEMIC EFFECT OF LYCIUM BARBARUM

Hyperglycemia, insulin resistance, and dyslipidemia are key metabolic disturbances found in MetS. Animal models that recreate these conditions have been extensively used to gain insight into the pathological mechanism and also to assess the protective effect of natural compounds against metabolic stress (Kottaisamy et al., 2021). In general, the antidiabetic properties of *L. barbarum* berries derivatives have been investigated on animals with induced beta cell toxicity through alloxan or streptozotocin treatment or animals fed a high-fat diet for at least 1 month. Zhao et al. (2015) studied the hypoglycemic and hypolipidemic effect of a crude *L. barbarum* extract and a DEAE cellulose purified fraction (IV) on 40 diabetic rats divided in 5 groups ($n = 8$): 50, 100 or 200 mg/kg of *L. barbarum* polysaccharides IV fraction; 100 mg/kg of crude polysaccharide extracts of *L. barbarum* and a control group. After diabetes induction through 6 weeks of high-fat diet and a single dose of streptozotocin, diabetic rats were treated with *L. barbarum* daily for 4 weeks by intragastric gavage. Both the crude polysaccharide extracts of *L. barbarum* and purified fraction at all doses were able to significantly reduce basal glycamia, glycated hemoglobin A1c, total cholesterol, triglycerides, and LDLc and to improve the response to an oral glucose tolerance test. This protective effect was associated with a lower mRNA expression of key genes involved in the regulation of energy metabolism in the liver, including phosphoenolpyruvate carboxykinase (PEPCK), sterol regulatory element-binding protein 1 (SREBP-1c), and fatty acid synthetase (FAS). Interestingly, the crude extract was equally effective as the purified fraction to reduce plasma metabolic biomarkers, and even it was more potent to reduce the liver expression of PEPCK, SREBP-1c, and FAS (Zhao et al., 2015). In a similar model of high-fat diet/streptozotocin induced diabetes in rats, Zhao et al. (2005) also reported a hypoglycemic effect of a *L. barbarum* extract associated with lower fasting insulin levels, reduction of postprandial glucose in an oral glucose tolerance test and an increased insulin sensitivity with a treatment of 10 mg/kg/day during 3 weeks. This outcome seems to be mediated at least in part by an increased translocation of GLUT4 to plasma membrane in response to insulin on skeletal muscle of *L. barbarum* treated rats (Zhao et al., 2005). Another evidences that could explain the mechanism underlying the hypoglycemic effect of *L. barbarum*, comes from studies using cell lines as models of relevant metabolic tissues. Caco2 cell line was used as a model of intestinal barrier to investigate the effect of an *L. barbarum* polysaccharide extract on the glucose uptake. In this cell model, *L. barbarum* reduced the passage of glucose across the Caco2 monolayer, suggesting that *L. barbarum* berry extracts could interfere with intestinal absorption of glucose (Tang et al., 2015). In the HepG2 hepatoma cell line, Zou et al. (2010) induced insulin resistance through incubation with a high dose of insulin and found that *L. barbarum* polysaccharide extract was able to rescue the insulin sensitivity as measured by an increase in glucose consumption. In the same study, it was reported that *L. barbarum* protected RINm5F insulinoma cells against alloxan oxidative damage (Zou et al., 2010). Therefore, there is preliminary evidence regarding the mechanism of hypoglycemic protection of *L. barbarum* berry extracts that points to inhibition of glucose transporters and antioxidant protection of beta cells, but further characterization of in vitro models will enable to identify molecular target(s) more precisely. Recently, Liu et al. (2022) reviewed the mechanisms involved in glycometabolism regulation by *L. barbarum* berries.

In summary, research studies have highlighted the ability of *L. barbarum* extracts to significantly reduce basal glycaemia and enhance glucose tolerance in diabetic animal models, offering potential avenues for hyperglycemia management. Additionally, *L. barbarum* extracts have demonstrated the capability to enhance insulin sensitivity, as evidenced by reduced fasting insulin levels and an improved response to insulin during glucose tolerance tests. Moreover, in vitro experiments have indicated that *L. barbarum* might inhibit intestinal glucose absorption, and its antioxidant properties may safeguard insulin-producing beta cells against oxidative damage. However, there is a need for substantial clinical data, standardized dosages and formulations, understanding potential interactions, and considering long-term safety aspects. In this sense, it has been shown that the consumption of goji juice in rats did not show toxicity at a maximum dose of 10 mL/kg/day (Amagase, 2008). These factors are vital for fully comprehending the practical applicability of *L. barbarum* in the treatment of hyperglycemia.

Dyslipidemia is a condition frequently associated with diabetes mellitus type 2. Besides, a chronic high-fat diet is a recognized triggering input for developing insulin resistance and diabetes mellitus type 2 in murine models. In this context, some studies focused on the effect of *L. barbarum* berry extracts in lipid metabolism in murine models. Pai et al. (2013) studied the hypolipidemic effect of *L. barbarum* on Wistar rats. Groups of 6 animals were fed on a cholesterol-rich high-fat diet for 15 days and then, they received an orally daily dose of 10, 20 mg/kg of *L. barbarum* or vehicle in control group, along with a high-fat diet for additional 30 days. Both doses of *L. barbarum* achieved a significant reduction in total cholesterol, triglycerides, and very-low-density lipoprotein cholesterol (VLDLc), but only the higher dose reduced LDLc. The positive hypolipidemic effect of *L. barbarum* had a similar magnitude than what was observed for atorvastatin treatment at 10 mg/kg/day (Pai et al., 2013). In a similar experimental model focused on oxidative damage induced by high-fat diet on rat liver, the administrations of *L. barbarum* aqueous and ethanolic extracts were able to reduce plasma levels of total cholesterol, LDLc, triglycerides, transaminases, and lipid peroxidation in liver (Cui et al., 2011). These results were consistent evidence obtained in male mice, where administration of *L. barbarum* polysacharides reduced LDLc, total cholesterol, and triglycerides in 10 animals fed a high-fat diet for 30 days (Ming et al., 2009). Future studies are needed to focus on isolating and characterizing the compounds of *L.*

TABLE 1 Bioactivities of *Lycium barbarum*-derived metabolites and their mechanisms of action.

Biological activity	Isolated metabolite	Type of study	Mechanism of action	Reference
Antidiabetic	Acidic polysaccharide fraction	In vitro: proliferation of RIN-m5f insulinoma cell line and glucose uptake in HepG2 and 3T3 cell lines	Increasing glucose metabolism and insulin secretion and promoting pancreatic β cell proliferation	Zhu et al. (2013)
		In vivo: oral administration of 125, 250, or 500 mg/kg/day of LBP-s-1to C57BL/6J mice		
	LBP3b fraction (Polysaccharide fraction obtained with ultrafiltration membranes separation and further purified by chromatography of DEAE cellulose column and Sephadex G-150)	In vitro: glucose passage through Caco2 cell monolayer in a transwell plate	Inhibition of the absorption of glucose in a dose-dependent manner	Tang et al. (2015)
	Polysaccharide fraction of fruit using hot water extraction and ethanol precipitation	In vitro: first- and second-phase secretion of glucagon-like peptide 1 (GLP1) in STC1 cells	Induction of GLP1 secretion	Zhao, Zhao et al. (2023)
		In vivo: first- and second-phase secretion of GLP1 in diabetic KKAy mice		
	Ultrasound-microwave combined extraction of leaf polysaccharides	In vitro: α-glucosidase and α-amilase enzyme inhibition	Inhibition of both enzymes	Quan et al. (2023)
	Phenolic amides	In vitro: α-glucosidase enzyme inhibition	Inhibition of α-glucosidase	Chen et al. (2023)
Anti-adipogenic	Water-soluble polysaccharides	In vitro: lipid accumulation, and expression transcription factors and proteins in the adipogenesis pathway in 3T3-L1 adipocytes	Downregulation of key transcription factors in the adipogenesis pathway, modulating lipid metabolism gene and protein expression levels	Wang et al. (2023)
		In vivo: progression of obesity and hyperlipidemia in obese mice		
Antitumor	Zeaxanthin-rich extract	In vitro: cytotoxicity, proliferation, and expression of stemness markers in BJ HEP fibroblast and in A375 melanoma cell lines	Upregulation of NK, ERK, p38, and the total NF-kβ toward an antiapoptotic pattern	Cenariu et al. (2021)
	Polysaccharide fractions with serial molecular weight	In vitro: viability, proliferation, apoptosis, and cell cycle progression of H22 hepatoma cell line	Induction of apoptosis, mitochondrial membrane potential destruction, and S phase arrest	Deng et al. (2017)
		In vivo: oral dose of 250 mg/kg/day in H22 tumor-bearing mice, during 10 days		

(Continues)

TABLE 1 (Continued)

Biological activity	Isolated metabolite	Type of study	Mechanism of action	Reference
Cytoprotective	Carotenoids-rich extract (lutein and zeaxanthin)	In vitro against beauvericin-induced cytotoxicity on Caco2 and on SH-SY5Y neuroblastoma cells	Possible interference with mitochondrial activity, prevent DNA damage, and to increase programed cell death	Juan-Garcia et al. (2019), Montesano et al. (2020), and Reddy et al. (2006)
Cardioprotective	Polysaccharides (glucose:fructose in a molar ratio of 1:2)	In vivo, using male Wistar rats treated with 150 or 300 mg/kg of LBP in a model of ischemia-reperfusion damage	Reduction of the myocardial lactate dehydrogenase level and increase the Na^+/K^+ ATPase and Ca^{2+} ATPase activities following heart ischemia-reperfusion injury	Hou et al. (2017), Lu and Zhao (2010)
			In addition, a decrease in the myocardial Bax-positive expression and the rate of myocardial cell apoptosis, along with an increase in Bcl-2-positive expression	
Hepatoprotective	Polysaccharides (mainly contained xylose and glucose, in addition to little amount of rhamnose, mannose, and galactose)	In vivo liver oxidative injury induced by high-fat diet on Kunming mice treated with an oral dose of 50, 100, or 150 mg/kg for 2 months	Decrease of blood and liver antioxidant enzymes activities and GSH level in model mice, increase of MDA level	Wu et al. (2010)
Immunomodulatory	Acidic polysaccharides	In vitro evaluated through phagocytic activity and NO production in RAW 264.7 macrophage cells	Increase of phagocytic activity of macrophages	Hao et al. (2020) and Xie et al. (2017)
			α-1,4-D-galactosiduronic was significantly affect the immunomodulation effects	
Antiaging	Polysaccharides	In vivo, using aged Kunming mice orally treated with 200, 350, or 500 mg/kg per day for 30 days	Increased endogenous lipid peroxidation and decreased antioxidant activities, as assessed by superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) and total antioxidant capacity (TAC), and immune function	Li et al. (2007)
Neuroprotective	Polysaccharides	In vivo, using Sprague–Dawley rats orally fed with 1 mg/kg 2 h before intermittent hypoxia	Promoting hippocampal neurogenesis and negatively modulating the apoptotic signaling cascades activated by oxidative stress and inflammation	Lam et al. (2015)
Antioxidant	Polysaccharides	In vitro methods, including superoxide radical (O_2^-) scavenging activity, reducing power, β-carotene linoleate model, and inhibition of mice erythrocyte hemolysis	Inhibitory activity in the β-carotene-linoleate model, superoxide scavenging ability, inhibition of mice erythrocyte hemolysis mediated by peroxyl free radicals, and also ferrous ion chelating potency	Li and Zhou (2007)
	Flavonoids (Rutin)	In vitro on myofibrillar proteins from minced mutton	Combination with free radicals produced by protein oxidation, block the free radical oxidation chain reaction, and inhibit the oxidation of myofibrillar proteins	Niu et al. (2021)

(Continues)

TABLE 1 (Continued)

Biological activity	Isolated metabolite	Type of study	Mechanism of action	Reference
	Phenolic compounds (gallic acid, chlorogenic acid, catechin, sinapinic acid, rutin, and carvacrol)	In vitro antioxidant capacity measured by DPPH radical scavenging, Trolox, and FRAP assays. Tyrosinase inhibition and anti-*Candida* activity	Radical scavenging ability	Mocan et al. (2019)
	Oil-in-water emulsions from seed oil	In vitro: antioxidant capacity measured by DPPH and ABTS radical scavenging and hydroxyl, and superoxide anion detoxification capability	Radical scavenging ability was elevated because emulsification increases seed oil dispersion	Liu et al. (2023)
Anti-osteoarthritic	Polysaccharides	In vitro in primary rat chondrocytes	Protection of chondrocytes through inhibiting DNA damage and apoptosis caused by H_2O_2 by activating the nuclear factor (erythroid-derived 2)-like 2 signaling pathways	Chen et al. (2020)

Abbreviations: NK, natural killer.

barbarum involved in hypolipidemic effects to understand their mechanisms of action, as well as their role in lipid metabolism pathways, such as cholesterol synthesis, uptake, and transport.

Although rats have been the most used model to assess the effect of *L. barbarum* on metabolic homeostasis, their hypoglycemic properties have also been demonstrated in other mammals (Agradi et al., 2021). In alloxan-induced diabetic mice, *L. barbarum* polysaccharides at 20 and 40 mg/kg for 28 days decreased fasting glycaemia, total cholesterol, and triglycerides (Jing et al., 2009). The protective effect of *L. barbarum* fruit water decoction (0.25 g/kg/day), crude *L. barbarum* polysaccharides (10 mg/kg/day), or purified *L. barbarum* polysaccharides (10 mg/kg/day) was investigated in 35 rabbits with alloxan-induced hyperglycemia (Luo et al., 2004). It was reported that there was a significant decrease in blood glucose, total cholesterol, and triglyceride levels in rabbits treated with all *L. barbarum* formulations, along with an increase HDLc. When comparing the three treatments, purified *L. barbarum* polysaccharides exhibited a more pronounced hypoglycemic effect than both water decoction and crude *L. barbarum* polysaccharides. However, its hypolipidemic effect appeared to be comparatively weaker (Luo et al., 2004). A more comprehensive analysis of energy homeostasis in rabbits in response to *L. barbarum* supplementation was performed in female rabbits during their reproductive cycle. In this study, rabbits were supplemented with 1% or 3% of the total energy for 4 weeks before artificial insemination. The 1% *L. barbarum* berries supplemented diet improved insulin sensitivity as reflected in a decrease in blood glucose, insulin, and HOMA (Menchetti et al., 2020). Other energy homeostasis markers, including body weight, body condition score, cortisol, and T3/T4 ratio, tended to improve with the 1% *L. barbarum* berries supplementation, but unexpectedly, the 3% supplementation increased insulin resistance (Menchetti et al., 2020). The protective effect of *L. barbarum* on metabolic disturbances elicited by preslaughter stress was studied in pigs. In this model, a supplementation of 1% with dried *L. barbarum* for 7 days reduced glycaemia and increase liver glycogen accumulation (Bai et al., 2016). The evidence in different animal models consistently shows that *L. barbarum* is capable to stabilize animals subjected to different metabolic stress conditions. Although one study in rabbits raise concerns about possible adverse metabolic effects of *L. barbarum* supplementation at high doses, this effect was exclusively found during pregnancy (Menchetti et al., 2020) but not in other conditions (Luo et al., 2004).

Another interesting approach to the potential uses of *L. barbarum* against MetS is its ability to modulate the intestinal microbiota. In this sense, the intragastric administration with *L. barbarum* extracts (1.04 or 2.08 g/kg) to diabetic rats during 4 weeks was found to regulate blood glucose and lipid levels, reduce proteinuria and transaminase levels, and ameliorate insulin resistance (Zhao et al., 2020). In the diabetic group, 45 bacterial genera were observed with significant differences compared to the control group, most of which belonged to *Firmicutes* and *Bacteroidetes*. Treatment with the extract was able to reverse the gut microbiota dysbiosis induced by diabetes. Similarly, treatment with *L. barbarum* polysaccharides (0.2% in drinking water) in obese mice was able to normalize dyslipidemia, decrease the number and size of adipocytes in epididymal adipose tissue, and downregulate the expression of adipogenic genes (Yang et al., 2021). Treatment with the extract also increased bacterial diversity, reduced the *Firmicutes*/*Bacteroidetes* ratio, and improved intestinal dysbiosis associated with obesity.

In humans, studies of *L. barbarum* berries supplementation are scarce and with a limited number of participants. A clinical trial (NCT02779985) studied the effect of the intake of 25 g of dried *L. barbarum* in a single dose, on the postprandial energy expenditure in 18 healthy overweight men (body mass index, BMI, between 25 and 30 kg/m^2), after a standardized meal. No significant changes in fat or sugar oxidation, postprandial triglyceride, or free fatty acid levels were found in response to a single dose of *L. barbarum* extract

(van den Driessche et al., 2019). It is important to note that previous studies had shown an acute increase in postprandial oxygen consumption in response to a single *L. barbarum* berries dose (Amagase & Nance, 2011); therefore, van den Driessche et al. (2019) designed their clinical trial to evaluate a possible increase in energy expenditure in an acute setting but no conclusions can be made regarding a long-term treatment with *L. barbarum* berry extracts. On the contrary Cai et al. (2015) studied the effect of *L. barbarum* polysaccharides supplementation for 3 months on 67 diabetes mellitus type 2 participants. The 37 participants who received 300 mg/body weight of *L. barbarum* polysaccharides per day presented a significant decrease in the area under de curve (AUC) in an oral meal tolerance test (OMTT) in comparison to the placebo-treated group and also an increase in the insulinogenic index (insulin-AUC/glucose-AUC). The hypoglycemic efficacy was stronger in those participants without hypoglycemic treatment. Serum lipids, including total cholesterol, triglycerides, HDLc, and apolipoprotein B, did not show significant changes throughout the treatment, but it should be noted that they were measured as AUC in an OMTT and no analysis was performed in fasting conditions (Cai et al., 2015). Interestingly, a significant decrease in the level of TNF-α was detected in the *L. barbarum* treated group, but not in other adipokines, including adiponectin, leptin, and IL-6 (Cai et al., 2015). Another study reported that the consumption of polysaccharides of *L. barbarum* (10 mg daily) during 4 weeks reduced insulin resistance, LDLc, total cholesterol, triglycerides, and malondialdehyde (MDA) and increased insulin release and HDLc in gestational diabetes mellitus patients (Yang et al., 2018). The mechanism of action evaluated in human pancreatic carcinoma cell SW1990 was related to an increase in ATP-binding cassette transporter A1 and a downregulation of SREBP-1c via miR-33. Although this study presents evidence showing an effective hypoglycemic outcome of *L. barbarum* in overweight/diabetic subjects, more studies in other populations are needed to confirm its protective effect. Besides, it would be interesting to study the preventive efficacy of *L. barbarum* berries in healthy people in long interventional studies. Finally, a study in which Yangyin Tiluo Decoction (400 mL daily, for 4 weeks) was administered, a traditional Chinese Herbal Formula containing *L. barbarum*, reduced the abundance of potentially pathogenic bacteria and lipoprotein in Chinese elderly patients with MetS (Ni et al., 2018). Among the most relevant, the treatment with the decoction reduced the abundance of genus Bacteroidales incertae sedis and species Enterobacteriaceae incertae sedis which were increased in the MetS patients. A mechanisms suggested through which *L. barbarum* regulates intestinal flora is by acting as a prebiotic, providing nourishment to beneficial gut bacteria (Ni et al., 2018; Xu et al., 2015).

6 | EFFECTS OF *Lycium barbarum* IN METS

The clinical and preclinical studies of the benefit effect of *L. barbarum* and its components, in MetS is diverse and include the effect of the berries, the *L. barbarum* polysaccharides and the xanthines as antioxidant, anti-inflammatory, hypoglycemic, and lipid-lowering compounds (described in Section 5). Figure 2 summarizes the main mechanisms involved in the protective effects of *L. barbarum* against MetS. Moreover, it is evident a high diversity of protocols of administration in doses and duration of the treatment.

For example, Zhu et al. (2015) registered that dose of 80 mg/kg/day for 30 days in mice (nine controls, nine high fatty diet, and nine high fatty diet + *L. barbarum* polysaccharides) prevented the increase of total triglycerides and cholesterol induced by high-fat diet. Moreover, reduced hepatic levels of MDA and HSP-70 and increases mRNA levels of CYP7A1 (cytochrome P450 gene), and activity of superoxide dismutase (SOD). At a systemic level, it also reduced plasmatic IL-6. The study included two additional groups with high-fat diet and chronic psychologic stress, where *L. barbarum* polysaccharides also showed beneficial effects. Also, in a murine model of aging induced by D-galactose, doses of 10 mL/100 mg/day of *L. barbarum* polysaccharides for 30 days reduced the D-gal induced increase of SOD, catalase (CAT), and GSH peroxidase (GSH-Px) activity (Yi et al., 2013). In streptozotocin-induced diabetes mellitus type 2 different doses of *L. barbarum* polysaccharides for 4 weeks (100 mg, 250, 500 mg/kg, $n = 8$ by group) increased the activity of SOD and GSH-Px in serum and reduced the level of IL-2, IL-6, TNF-α, interferon (IFN)-γ, monocyte chemoattractant protein 1 (MCP-1), and intercellular adhesion molecule. The improvement in oxidative and inflammatory status was companied by less albuminuria and blood urea nitrogen concentration. The changes were associated with a reduction in the expression of phosphorylated nuclear factors kappa B and the inhibitor kappa B alpha in the kidney (Du et al., 2016). In a similar study, Li (2007) studied the effect of lower doses of *L. barbarum* polysaccharides for 30 days in streptozotocin-treated rats (10 control vs. 40 diabetics, treated daily with 0, 50, 100, and 200 mg *L. barbarum* polysaccharides/kg). They found an increase in blood SOD activity and MDA levels in *L. barbarum* polysaccharides-treated diabetic rats, companied by normalization in serum triglycerides, LDLc, but only with higher *L. barbarum* polysaccharides doses insulin and glucose were normalized. Moreover, in liver and kidney, also activity of antioxidant enzymes GSH-Px and CAT was normalized by *L. barbarum* polysaccharides treatments (Li, 2007). In another study, where diabetes was induced by alloxan, the *L. barbarum* polysaccharide galactomannan in dose of 500 mg/kg/day for 21 days, was able to prevent weight lowering, and changes in lipid profile, including decreasing in triglycerides, LDLc, VLDc, and increasing in HDLc. Also, normalized CAT, SOD, GSH-Px, GSH, MDA, creatinine, and aspartate aminotransferase (AST), indicating protection at systemic, hepatic, and renal levels (Al-Fartosy, 2015). In this study, six animals were used by group and additionally, registered that no mortality was presented in doses as higher as 1 g/kg until 72 h. Similar protective results were found by Wu et al. (2010) in rats fed on high-fat diet, who found that *L. barbarum* polysaccharides normalized blood glucose, lipids, and oxidative status in a dose-dependent way when was administrated in doses of 50–100-150 mg/kg/day, $n = 5$ by group) (Wu et al., 2010).

In human studies (Table 2), the antioxidant effect of a characterized *L. barbarum* berries juice (GoChi) was evident in healthy adults between 55 and 72 years of age (25 controls vs. 25 treated). Serum activities of antioxidant enzymes SOD and GSH-Px were increased after 30 days of

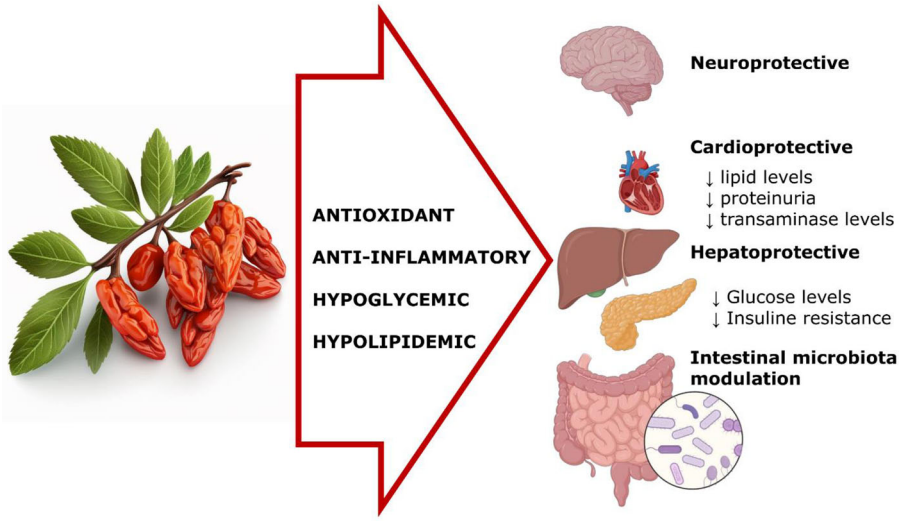

FIGURE 2 Protective mechanisms of *Lycium barbarum* L. against metabolic syndrome (MetS).

TABLE 2 Clinical studies of *Lycium barbarum* L.

Type of study	Participants	Treatment	Results	Reference
Randomized, double-blind, and placebo-controlled trial	Fifty Chinese healthy adults (55–72 years; 25 control vs. treated)	120 mL daily of GoChiTM (*L. barbarum* berries) for 30 days	Increased serum activity of antioxidant enzymes SOD (8.4%) and GSH-Px (9.9%), decreased MDA levels (8.7%)	Amagase et al. (2009)
Randomized, double-blind, and placebo-controlled trial	Forty-two healthy males (20–40 years; 21 control vs. 21 treated)	300 mg/*L. barbarum* polysaccharides capsules for 4 weeks	Reduced triglyceride/HDLc index	Xia et al. (2018)
Randomized, double-blind, and placebo-controlled trial	Taekwondo athletes (18–22 years; 23 control vs. 23 treated)	0.72 mg/day *L. barbarum* polysaccharides capsules for 6 weeks	Reduced MDA levels, increased SOD and CAT activity, improved CD4+/CD8+ lymphocyte ratio, enhanced NK cells, increased immunoglobulin G and A levels	Ma, Zhang, Yang et al. (2019)
Randomized, double-blind, and placebo-controlled trial	Fifty subjects with Metabolic Syndrome (25 control, 49.2 ± 2,6 years vs. 25 treated, 52.6 ± 2.2 years)	14 g *L. barbarum* berries daily for 45 days	Reduced TBARS levels, increased GSH plasma, improved CAT and SOD activity in red blood cells, normalized lipid profile, hepatic function, and inflammatory markers, reduced waist circumference by 6.3 cm	de Souza Zanchet et al. (2017)

Abbreviations: CAT, catalase; GSH, glutathione; GSH-Px, glutathione peroxidase; HDLc, high-density lipoprotein cholesterol; MDA, malondialdehyde; NK, natural killer; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances.

daily consumption of 120 mL of GoChi, as did a decrease in MDA levels (Amagase et al., 2009). In another study carried out in 42 healthy subjects, the intake of 300 mg of *L. barbarum* polysaccharides significantly reduced triglyceride/HDLc index, a predictor of type 2 diabetes and cardiovascular disease (Xia et al., 2018). Moreover, the administration of *L. barbarum* polysaccharides in capsules (0.72 mg/day) for 6 weeks reduced MDA level and increased SOD and CAT activity in the blood of taekwondo athletes (23 control vs. 23 treated) (Ma, Zhang, Yang et al., 2019). Moreover, in this case, the treated group improved the relation CD4+/CD8+ lymphocytes, the natural killer population, and the level of immunoglobulin G and A. Another clinical randomized trial was conducted in 50 subjects with MetS, half of whom received 14 g of *L. barbarum* berries for 45 days in reduced thiobarbituric acid reactive substances levels and increase GSH plasma and improved CAT and SOD activity in red blood cells. Moreover, lipid profile (triglycerides, LDLc, VLDLc, and HDLc), hepatic function (AST and alanine aminotransferase), and inflammatory markers were normalized (TNF-α, MCP-1, and CRP). Moreover, waist circumference was reduced by 6.3 cm, which evidences an important anthropometric improvement (de Souza Zanchet et al., 2017).

7 | CONCLUSIONS AND UPCOMING PERSPECTIVES

Today, no one doubts that MetS is a growing disorder in all countries and is an important socio-sanitary problem. Accordingly, there is increasing interest in creating novel therapeutic approaches that could target multiple components of MetS and achieve a comprehensive treatment procedure. Developing a drug that decreases inflammation, and lowers plasma lipids, blood pressure, and blood glucose levels and normalizes gut dysbiosis could be optimal for the management of metabolic diseases. Presently, there are no accepted drugs that can safely and permanently reduce multiple conditions connected with MetS. This review summarizes the multiple therapeutic actions of *L. barbarum* that may be considered for the treatment of MetS. However, there are a limited number of studies related to the effect of *L. barbarum* in MetS, which demonstrated effectiveness in the treatment of obesity, diabetes mellitus type 2, and prevention of complications of this disease. Moreover, the *L. barbarum* extracts showed low toxicity or adverse effects, in the spite of high diversity of methods of extraction and doses used. When analyzing the results obtained, especially in vitro and in animal models, it can be concluded that the underlying mechanisms of action are not yet completely elucidated and appear to be multifactorial. The administration of *L. barbarum* induces an increase in antioxidant defense mechanisms and a reduction in inflammatory cytokines associated with the inhibition of the NFKb pathway. Furthermore, *L. barbarum* is related to a downregulation of adipogenic genes, an increase in GLUT4 translocation in the muscle, and a modulation of the intestinal microbiota that is reflected with a decrease in the *Firmicutes/Bacteroidetes* ratio. Therefore, more research related to the hypoglycemia, lipid-lowering, and antioxidant effect of *L. barbarum* and its components should be performed, especially randomized clinical trials with higher size samples that including with food intake recording. In addition, future studies on bioavailability of *L. barbarum* components need to be conducted to better understand its bioactivity.

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CONFLICT OF INTEREST STATEMENT

No competing interest.

ORCID

Javad Sharifi-Rad https://orcid.org/0000-0002-7301-8151

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