Tropical Journal of Pharmaceutical Research November 2024; 23 (11): 1939-1947
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i11.19

Review Article

An overview of the hypolipidemic effect of *Genus Berberis*

María Cristina Furrianca[1,2,3,4]* Veronica Ulloa[2,3], Héctor Sandoval[5], Hector Retamal-Matus[2,3,6], Alejandra Fernández-Elgueta[2,3,6], Juan Carlos Borquez[2,3,6,7]

[1]Departamento de Enfermería, [2]Facultad de Ciencias de la Salud, [3]Universidad de Magallanes– UMAG; [4]Centro Interuniversitario de Envejecimiento Saludable – CIES; [5]Ingeniero Forestal, Experto en Análisis Espacial y Medio Ambiente; [6]Departamento de Kinesiología, [7]Laboratorio de Investigación en Nutrición y Actividad Física (LABINAF), Instituto de Nutrición y Tecnología de los Alimentos (INTA), Universidad de Chile, Santiago, Chile

For correspondence: **Email: maria.furrianca@umag.cl*

Sent for review: 17 May 2024 *Revised accepted: 2 November 2024*

Abstract

Dyslipidemia is a chronic disease characterized by elevated blood lipid levels treatable with statins. However, long-term statin use may have adverse effects, such as liver damage and memory loss. Nevertheless, plants and their active compounds effectively and safely improve lipid profiles. This review aims to update information on the genus Berberis as a hypolipidemic agent, assess the effects of these extracts on organisms and provide evidence supporting the use of these natural products in pharmaceutical drugs. Berberis species with therapeutic potential include B. vulgaris, B. integerrima, B. aristata, B. lycium, B. orthobotrys, and B. calliobotrys, which have shown promising results in reducing lipid levels in humans and other animals. In addition, combining berberine with nutraceuticals may improve its intestinal absorption, enhancing its lipid-lowering effect. Herbal medicine studies suggest that Berberis has a high potential for the management of hyperlipidemia.

Keywords: *Lipid profile, Hypolipidemic, Dyslipidemia, Cholesterol, Plant extracts, Traditional uses, Berberis*

Tropical Journal of Pharmaceutical Research is indexed by Scopus, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Dyslipidemia is a chronic metabolic disease characterized by increased total cholesterol (TC) and low-density lipoprotein (LDL-C) cholesterol and triglyceride (TG) levels, as well as decreased high-density lipoprotein cholesterol (HDL-C) levels [1,2]. Currently, lovastatin and atorvastatin statins are used as the first-line treatment to improve lipid profiles (Total cholesterol, Low-density lipoprotein cholesterol, High-density lipoprotein cholesterol, Triglycerides) [3]. However, long-term, high-dose statin use has mild (such as headache, nausea, constipation and muscle pain) and severe (including liver damage, rhabdomyolysis, kidney failure, and memory loss or damage) side effects [4–6]. Considering these complications, researchers must identify alternative treatments for dyslipidemia.

Plants and their active compounds effectively and safely improve lipid profiles [7–10]. Several studies on plant extracts with lipid-lowering activity have highlighted their ability to improve lipid profile parameters and fatty liver [11–13]. Therefore, this review aims to update information on the genus *Berberis* as a hypolipidemic agent,

assess the effects of these extracts on various organisms and promote the application of these natural products in pharmaceutical drugs.

METHODS

A comprehensive review of the scientific literature on *Berberis* species and their hypolipidemic effects was conducted. The search utilized databases such as Scopus, PubMed and Google Scholar, employing keywords including *Berberis*, dyslipidemia, obesity, hypolipidemic, ethnopharmacology, ethnobotany, metabolic diseases, metabolic syndrome and diabetes. No restrictions were applied regarding the language, publication year, or type of articles (original research, review articles). Additionally, the reference lists of the selected articles were examined to identify further relevant studies. It is important to note that this review does not constitute a systematic review.

Using plants of the genus *Berberis* to treat diseases

The family Berberidaceae encompasses approximately 650 species and 17 genera of plants used in folklore and in various traditional medicine systems, including the genus *Berberis* [14]. *Berberis* stands out for its use in traditional medicine in eastern countries, such as China, India, Turkey and Iran, to treat diseases associated with kidney stones, rheumatism, fever, morning sickness, jaundice and cholecystitis, as well as other diseases [15–17]. Thus, while this genus is distributed worldwide, the main pharmacological applications of *Berberis* have been studied with species distributed in Asia [18].

Several *Berberis* (B.) species with medicinal uses are found in the literature. However, the most prevalent species with lipid-lowering activity are *B. vulgaris*, *B. integerrima*, *B. aristata*, *B. lycium*, *B. orthobotrys* and *B. calliobotrys*. These species have other medicinal uses, as *B. vulgaris* plants are widely used to treat bile and liver diseases [19] and *B. integerrima* plants are used to treat fever, diabetes, jaundice and high blood pressure [20]. *Berberis aristata* plants are used as antihepatotoxic, antibacterial, antihyperglycemic, antioxidant, antimicrobial, antipyretic, anticancer and antilipidemic agents [21]. Furthermore, *B. lycium* plants have antihyperlipidemic, antidiabetic, antibacterial and antifungal properties [22], *B. orthobotrys* plants show antihypertensive and lipid-lowering activity [23] and *B. calliobotrys* plants are used to treat pharyngitis, fever, back pain and jaundice [24]. Among the studies on *Berberis* species, lipid-lowering activity has been examined in two humans and other animals.

Key *Berberis* species that improving lipid profile in humans

Berberis vulgaris, *B. integerrima* and *B. aristata* are the most commonly used *Berberis* species in critical trials. As reported in a meta-analysis of 5 randomized controlled trials with 339 participants, supplementation with *B. vulgaris* significantly decreased TC (23.58 mg/dL), TG (29.16 mg/dL) and LDL-C (13.75 mg/dL) levels, albeit with no significant change in HDL-C (3.40 mg/dL). Most likely, *B. vulgaris* extracts activate peroxisome proliferator-activated receptor alpha (PPAR-α). This nuclear receptor protein functions as a transcription factor and is mainly expressed in tissues that metabolize fatty acids (the liver, heart, kidney, and muscles). Accordingly, *B. vulgaris*-induced PPAR-α activation may decrease serum TG levels and increase HDL-C levels [25].

Another lipid-lowering mechanism of *B. vulgaris* may involve berberine, a secondary metabolite that decreases lipid droplet accumulation in preadipocytes and inhibits terminal adipocyte differentiation. These effects are associated with PPAR-γ2 mRNA downregulation, which decreases TG and lipid storage [25]. In a clinical trial involving patients with type 2 diabetes mellitus (DM-2), variations were observed in the treatment group before and after the intervention with the extract. However, the results showed that TC and LDL-C levels significantly decreased by 9.44 % and 8.65 %, respectively, and the HDL-C levels increased by 5.23 %. The berberine concentration was estimated at 78.65 mg/500 mg of dry extract. Therefore, lipid profiles may improve because *B. vulgaris* extracts contain berberine, which lowers TG, TC, and LDL levels [26].

According to Kermani and co-workers, *B. vulgaris* fruit extracts may improve some metabolic syndrome parameters by significantly decreasing the systolic blood pressure and waist circumference of patients when comparing these parameters before and after treatment. However, no significant differences were found in lipid profiles when the parameters were compared between the same study groups. Also, the TG, TC, LDL and HDL levels increased after treatment with the extract. Moreover, a significant decrease in serum cholesterol levels was observed in the placebo group but not in the treatment group. Nevertheless, the authors flagged some study limitations, such as the small

sample size (n = 50) and short study period (21 days).

Another species used to control lipid profiles is *B. integerrima*. This species is crucial in lowering TG levels and improving fatty liver disease, as shown in a previous study [27]. The authors conducted a clinical trial with patients that had hypertriglyceridemia and fatty liver and assessed the effect of *B. integerrima* extracts for 45 – 60 days. After this period, they observed a significant decrease in blood TG levels in 31.50 and 32.17 % of men and women, respectively. As for fatty liver disease, enzyme levels improved after the treatment in 21 patients [27]. Also, in patients with nonalcoholic fatty liver, the authors demonstrated that *B. integerrima* (fruit) extracts significantly decreased TC, TG and LDL-C levels by 17.81, 13.28 and 15.57 %, respectively, when comparing patients before and after the treatment. In addition, they recorded a significant increase in HDL-C levels of 18.17 %, potentially due to the increase in total antioxidant capacity and the levels of the enzyme glutathione peroxidase contained in the extract [28].

After treatment with *B. integerrima* for 3 months, patients with active rheumatoid arthritis showed a significant decrease in body fat percentage (2.96 %). Serum parameters (TC, TG, and LDL) also decreased but only significantly for LDL (119.16 *vs* 108.71 mg/dL). Conversely, HDL-C levels were significantly higher in the treatment group than those in the placebo group (65.97 *vs* 57.55 mg/dL) [29]. The authors indicated that patients with rheumatoid arthritis have a normal lipid profile. In contrast, several studies have demonstrated that berberine improves hyperlipidemia by stimulating fatty acid oxidation and restoring the metabolic profile through liver and muscle AMP-activated protein kinase (AMPK) activity [30-34].

Berberis improves lipid profiles in animals with dyslipidemia

High serum lipid levels are associated with diseases such as DM-2 and fatty liver. For this reason, most animal studies have generated a diabetic or hyperlipidemic model to validate diverse types of *Berberis* extracts. The *Berberis* species most commonly used in animal studies are *B. vulgaris*, *B. orthobotrys*, *B. integerrima*, *B. lycium*, *B. aristate,* and *B. calliobotrys.* Meliani *et al* conducted a study with streptozotocin-induced diabetic rats, noting that the group of diabetic rats treated with *B. vulgaris* root extract had significantly lower TG (35.61 %) and TC (49 %) levels than the group of untreated diabetic rats [35]. The authors reported that the extract also had significant hypoglycemic effects, possibly due to the activity of secondary metabolites, such as tannins, saponins, flavonoids, alkaloids and steroids. Upon treatment with *B. vulgaris* extract, TG and VLDL levels significantly decreased by 62.9 and 62.5 % with 25 mg/kg extract, and by 64.4 and 64.06 % with 100 mg/kg extract, respectively. However, TC, LDL-C and HDL-C levels showed no significant differences when comparing the treated and untreated groups at both concentrations. Diabetic rats treated with *B. vulgaris* also show elevated adiponectin levels at both extract concentrations [36].

Torkamaneh and his group demonstrated that *B. vulgaris* extract significantly decreased lipid levels in diet-induced obese rats [37]. The TC, TG and LDL levels were 39.95, 35.88 and 37.75 % lower in the high-calorie diet group treated with the *B. vulgaris* extract than those in the high-calorie diet group without treatment, respectively. In addition, the results showed a 43.32 % increase in HDL levels and a significant decrease in aspartate (AST) and alanine (ALT) transaminase levels of 76.38 and 31.72 % in the group treated with the *B. vulgaris* extract. When assessing the combination of exercise with *Berberis* extract intake, these authors found slightly better results, albeit with non-significant differences between treatments [37].

In another report, *B. vulgaris* extracts was shown to significantly decrease the levels of rat liver enzymes [38]. In this study, ALT and alkaline phosphatase (ALP) levels were 48.10 and 61.91 % lower in the hypercholesterolemic group treated with 300 mg/kg of *B. vulgaris* extract than those in the hypercholesterolemic group without treatment, respectively. This effect may derive from the antioxidant properties of this plant, which is a good option to improve liver function [38]. The lipid-lowering effect of *B. vulgaris* was also demonstrated by other authors who found that TC and TG levels were 22.84 and 26.69 % lower in hyperlipidemic rats treated with 300 mg/kg extract for one month than in untreated hyperlipidemic rats, respectively [39].

Berberis integerrima root extracts also have positive effects in improving lipid profiles. Lipid levels were significantly lower in streptozotocin-induced diabetic rats after six weeks of treatment with 250 and 500 mg/kg of the extracts than in their counterparts without treatment. At 250 mg/kg, *B. integerrima* root extracts significantly decreased TC (39.17 %), TG (29.93 %) and LDL-C (69.63 %) levels and also significantly increased HDL-C (128.76 %) levels. Furthermore, these extracts at 500 mg/kg

significantly decreased TC (44.83 %), TG (39.31 %), and LDL-C (80.02 %) levels and significantly increased HDL-C (157.95 %) levels. In both treatments, liver enzyme, including ALP, ALT and AST levels, decreased by 18.49 %, 26.28 % and 42.52 % upon treatment with 250 mg/kg and 43.82, 50.36 and 50.71 % upon treatment with 500 mg/kg *B. integerrima* root extract, respectively. Although the mechanism of action of *B. integerrima* extracts remains unknown, it is plausible that they lower lipid levels by improving insulin action [40]. *Berberis integerrima* fruit extracts also significantly decreased lipid levels in alloxan-induced diabetic rats, with TC, TG and LDL levels decreasing by 57.93, 42.90 and 81.58 %, respectively [41].

Berberis lycium plants have been studied for their antihyperglycemic and antihyperlipidemic effects. In a study conducted in alloxan-induced diabetic rats, Ghazanfar *et al* observed that serum lipid levels were significantly lower in diabetic rats treated with 500 mg/kg *B. lycium* extract than in diabetic rats without treatment [42]. The results indicated that aqueous and methanol *B. lycium* extracts significantly decreased TC (36.10 and 31.76 %), TG (54.69 and 46.20 %), VLDL-C (46.71 and 38.51 %) and LDL-C (48.46 and 51.29 %) levels [42]. Also, Zaib *et al* demonstrated that 500 mg/kg *B. lycium* stem extracts significantly decrease TC (11.16 %) and TG (33.69 %) levels and increase HDL-C (33.15 %) levels, potentially by improving insulin secretion and action as the hormone decreases lipid levels in diabetic rats [43]. At the same concentration (500 mg/kg), *B. lycium* stem extracts also significantly decrease ALP (35.95 %), ALT (40.81 %) and AST (40.47 %) levels, which may be attributed to liver cell regeneration and cell membrane maintenance [43].

Berberis aristata has hypolipidemic effects, improving lipid levels. In a study conducted by Upwar *et al*, *B. aristata* extracts were tested in streptozotocin-induced diabetic mice. At 500 mg/kg, these extracts significantly decreased TC (45.48 %) and TG (51.09 %) levels. Even at 250 mg/kg, these extracts also significantly decreased TC (37.8 %) and TG (42.58 %) levels, perhaps because this extract increases the activity of enzymes involved in the synthesis and excretion of bile acids [44]. Furthermore, Razzaq and co-workers assessed the effect of 25 mg/kg *B. aristata* extracts in rabbits fed a high-cholesterol diet for 30 and 45 days. These extracts significantly decreased TC, TG and LDL-C levels after 30 and 45 days, respectively, possibly because they contain berberine, a compound that can induce blood vessel relaxation [45]. This vasodilator effect is crucial in the treatment of metabolic diseases associated with stroke.

Berberis orthobotrys extracts also have an antihyperlipidemic effect in rats. In a study with high-fat diet-induced hyperlipidemic rats, researchers assessed the effect of *B. orthobotrys* extracts at two concentrations (50 and 100 mg/kg). When comparing groups treated with *B. orthobotrys* extracts at these doses with the control group (high-fat diet), they observed a significant decrease in lipid parameters after both treatments. In particular, 100 mg/kg *B. orthobotrys* extract significantly decreased TC (48.33 %), TG (89.35 %) and LDL-C (38.27 %) levels while also significantly increasing HDL-C levels (29.86 %) [46].

Another species with lipid-lowering potential is *B. calliobotrys*. At 600 mg/kg, *B. calliobotrys* extracts decreased lipid levels in alloxan-induced diabetic rats. TC (36.02 %), TG (44.33 %), and LDL-C (54.93 %) levels were lower and HDL-C (66 %) levels were higher in these diabetic rats than those in diabetic control rats [47].

Combining *Berberis* with nutraceuticals improves its intestinal availability

One of the main problems of *Berberis* extracts is their low intestinal availability. To improve its intestinal absorption and hence bioavailability, *Berberis* extracts have been combined with other herbal extracts. Among these combinations, Berberol® stands out as a commercial product mixing extracts of *B. aristata* and *Silybum marianum*. The latter species is known to improve the intestinal absorption of *Berberis* by inhibiting the transmembrane protein P-glycoprotein (P-GP) [48].

In a study conducted with this nutraceutical, Di Pierro and his group assessed the efficacy of using Berberol® in comparison with *B. aristata* to treat patients with DM-2. The authors observed that TC, TG and LDL-C levels decreased by 11.04, 22.58 and 16.97 % in the group treated with Berberol® and 11.96, 21.18 and 12.12 % in the group treated with *B. aristata* extract, respectively. When comparing the two treatments, no significant differences were seen in lipid levels, which may be explained by differences between study populations, treatments and inclusion criteria. Nevertheless, glycated hemoglobin (HbA 1c) levels were significantly lower in the group treated with Berberol® than in the group treated with *B. aristata* extract. This finding may indicate that Berberol® improves glycemic status in patients with DM-2.

The efficacy of Berberol® was also assessed in a randomized, placebo-controlled, clinical trial with dyslipidemic patient's intolerant to statins at high dosages. Metabolic parameters were determined after 3 and 6 months. The trial demonstrated that administering Berberol® with statins at low dosages lowers lipid levels when compared to treatment and placebo groups. Additionally, the parameters worsened after decreasing the statin dosages [49]. More recently, as shown in a randomized controlled trial comparing patients with type 1 diabetes mellitus (DM-1) before and after treatment with Berberol®, the dietary supplement significantly decreased total insulin and glycated hemoglobin levels. The lipid profile recorded a significant decrease in TC (17.55 %), TG (19.46 %) and LDL-C (26.29 %) levels as well as an increase in HDL-C (6.18 %) levels. These results suggest that *S. marianum* helps to improve not only the intestinal availability of *B. aristata* but also parameters of the lipid profile, potentially through a synergistic effect of both extracts. *Silybum marianum* likely inhibits cholesterol acyltransferase, reducing cholesterol absorption and lipoprotein biosynthesis [50].

Other studies have also assessed the efficacy of Berberol® K, which consists of berberine, silymarin cum monacolins K and KA. Monacolins reversibly inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [51]. In patients with low cardiovascular risk, treatment with Berberol® K significantly decreased parameters of the lipid profile, namely TC (22.9 %), TG (21.0 %) and LDL-C (31.6 %) [48]. In patients with dyslipidemia, Di Pierro and his group compared treatment using Berberol® K and treatment with Lovastatin [52]. The results showed that TC, TG and LDL-C levels were significantly decreased after both treatments, but treatment with Berberol® K led to higher reduction percentages (28.8, 19.05 and 28.8 % for TC, TG and LDL-C, respectively). Therefore, Berberol® K may be an alternative for patients who perceive statins negatively and who prefer a natural treatment as a complementary treatment.

In another study, Berberol® K efficacy was retrospectively evaluated in diabetic patients with dyslipidemia by comparing patients at baseline with patients after 6 months of treatment. The results showed a significant decrease in TC (23.32 %), TG (18.77 %) and LDL-C (30.76 %) levels and a significant increase in HDL-C (4.79 %). These effects may be due to an increase in LDL receptor expression induced by berberine and also to the inhibitory effect of monacolins K and KA on HMG-CoA reductase. Therefore, berberine and monacolins K and KA synergistically affect proprotein convertase subtilisin/kexin type 9 (PCSK9) [53].

Treatment efficacy was also compared between *B*. *aristata/S. marianum* and metformin in patients with DM-2 after 6 months. In both treatment groups, lipid parameters decreased significantly, especially in the group treated with *B. aristata/S. marianum,* who had lower lipid levels (17.87 % TC, 26.68 % LDL-C and 12.08 % TG) than patients treated with metformin (7.42 % TC, 10.85 % LDL-C and 6.43 % TG) [54]. In a pilot clinical trial, short-term effects of dry extracts of *Cynara scolymus* and *B. aristata* were assessed in patients with moderate hypercholesterolemia in primary prevention for cardiovascular disease. After two months of treatment, the nutraceutical significantly decreased plasma TC (19.10 %), TG (15.71 %) and LDL-C (15.82 %) levels in association with a standardized control diet [55].

Another combination of active compounds, primarily consisting of red yeast rice extract, berberine, policosanol, folic acid, coenzyme Q_{10} and astaxanthin, has been tested in a multicenter study with 1,751 participants assessing the combined effect of these nutraceuticals in hyperlipidemic patients. After 16 weeks, the group of patients treated with these nutraceuticals in association with diet showed a constant and significant improvement in lipid parameters with TC (19.1 %), LDL-C (23.5 %), TG (17.9 %) in comparison with the group of patients receiving diet alone with TC (9.4 %), LDL (10.8 %) and TG (11.3 %) [56]. The same combination of nutraceuticals was also studied in hypercholesterolemic patients (> 75 years) for one year. The results showed a significant decrease in TC (20 %) and LDL-C (31 %) levels in comparison with baseline levels [57]. In another study, treatment with a berberine/ policosanol/ red yeast rice extract (BBR/P/RR) mixture was compared with treatment with ezetimibe (EZE) in hypercholesterolemic patients. The LDL levels decreased by 31.7 % in patients treated with BBR/P/RR and 25.4 % in patients treated with EZE [58].

A meta-analysis of 14 randomized controlled trials showed that the nutraceutical product, NComb, composed of red yeast rice extract, berberine, policosanol, astaxanthin, coenzyme Q_{10} and folic acid, decreased plasma TC (26.15 mg/dL), LDL-C (23.85 mg/dL) and TG (13.83 mg/dL) levels and increased HDL-C levels (2.53 mg/dL) [59]. A multicenter study involving patients with moderate hypercholesterolemia also highlighted the variable LDL-C response to

the supplementation with Armolipid Plus (policosanol, red yeast rice extract, berberine, coenzyme Q_{10}, folic acid and astaxanthin), which may be linked to three polymorphisms in the 3′ UTR 1944 region of LDLR and two in the 5′ UTR region 1944 of PCSK9 [60].

CONCLUSION

In traditional medicine, *Berberis* species have been used to treat various diseases. These species are distributed worldwide and mainly used for medicinal purposes in Asian. While several species used in traditional medicine have been described in the literature, primarily six species are currently being tested in clinical trials, aimed at validating their lipid-lowering effect, namely *B. vulgaris*, *B. integerrima*, *B. aristata*, *B. lycium*, *B. orthobotrys* and *B. calliobotrys*.

Most human and animal studies analyzed in this review have reported promising results, validating the use of *Berberis* species in the treatment of hyperlipidemia because they significantly decrease lipid levels. Furthermore, some clinical trials have combined berberine with nutraceuticals aimed at improving the intestinal availability of this extract, reporting decreased lipid levels. Based on this literature review, *Berberis* is a genus that offers wide range of opportunities and high potential in herbal medicine.

DECLARATIONS

Acknowledgements

None.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

REFERENCES

1. *Cicero AFG, Colletti A. Combinations of phytomedicines with different lipid lowering activity for dyslipidemia management: The available clinical data. Phytomed 2016; 23: 1113–1118.*
2. *Chang AY, Abou-Arraj NE, Rodriguez F. Interventions to reduce ethnic and racial disparities in dyslipidemia management. Curr Treat Options Cardiovasc Med 2019; 21: 24.*
3. *Ray S. Role of statins in the management of dyslipidaemia. Indian Heart J 2024; 76: S33–S37. https://www.sciencedirect.com/science/article/pii/S0019483223004583.*
4. *Zarei A, Changizi-Ashtiyani S, Taheri S, Ramezani M. A quick overview on some aspects of endocrinological and therapeutic effects of Berberis vulgaris L. Avicenna J Phytomed 2015; 5: 485–497.*
5. *Allen SC, Mamotte CDS. Pleiotropic and adverse effects of statins—Do epigenetics play a Role? J Pharmacol Exp Ther 2017; 362: 319 LP – 326.*
6. *Pinal-Fernandez I, Casal-Dominguez M, Mammen AL. Statins: pros and cons. Med Clínica 2018; 150: 398–402.*
7. *Belwal T, Bisht A, Devkota HP, Ullah H, Khan H, Pandey A, Bhatt ID, Echeverría J. Phytopharmacology and clinical updates of Berberis species against diabetes and other metabolic diseases. Front Pharmacol 2020; 11: 41.*
8. *Sham T-T, Chan C-O, Wang Y-H, Yang J-M, Mok DK-W, Chan S-W. A review on the traditional chinese medicinal herbs and formulae with hypolipidemic Effect. Singhal SS, Editor. Biomed Res Int 2014; 2014: 925302.*
9. *Tappia PS, Xu Y, Dhalla NS. Reduction of cholesterol and other cardiovascular disease risk factors by alternative therapies. Clin Lipidol 2013; 8: 345–359.*
10. *Lin H-H, Charles AL, Hsieh C-W, Lee Y-C, Ciou J-Y. Antioxidant effects of 14 Chinese traditional medicinal*

herbs against human low-density lipoprotein oxidation. J Tradit Complement Med 2015; 5: 51–55.
11. Ji X, Shi S, Liu B, Shan M, Tang D, Zhang W, Zhang Y, Zhang L, Zhang H, Lu C, et al Bioactive compounds from herbal medicines to manage dyslipidemia. Biomed Pharmacother 2019; 118: 109338.
12. Fu C, Jiang Y, Guo J, Su Z. Natural products with anti-obesity effects and different mechanisms of action. J Agric Food Chem 2016; 64: 9571–9585. https://doi.org/10.1021/acs.jafc.6b04468.
13. Tabatabaei-Malazy O, Larijani B, Abdollahi M. Targeting metabolic disorders by natural products. J Diabetes Metab Disord 2015; 14: 57.
14. Mohi-ud-din R, Mir RH, Mir PA, Farooq S, Raza SN, Raja WY, Masoodi MH, Singh IP, Bhat ZA. Ethnomedicinal uses, phytochemistry and pharmacological aspects of the Genus Berberis Linn: A comprehensive review. Comb Chem High Throughput Screen 2021; 24: 624–644.
15. Srivastava S, Srivastava M, Misra A, Pandey G, Rawat A. A review on biological and chemical diversity in Berberis (Berberidaceae). EXCLI J 2015; 14: 247–267. https://pubmed.ncbi.nlm.nih.gov/26535033.
16. Bhardwaj D, Kaushik N. Phytochemical and pharmacological studies in genus Berberis. Phytochem Rev 2012; 11: 523–542. http://dx.doi.org/10.1007/s11101-013-9272-x.
17. Khan I, Najeebullah S, Ali M, Shinwari Z. Phytopharmacological and ethnomedicinal uses of the Genus Berberis (Berberidaceae): A review. Trop J Pharm Res 2016; 15: 2047–2057.
18. Salehi B, Ata A, Kumar NVA, Sharopov F, Ramírez-Alarcón K, Ruiz-Ortega A, Ayatollahi SA, Tsouh Fokou P, Kobarfard F, Zakaria AZ, et al Antidiabetic potential of medicinal plants and their active components. Biomolecul 2019; 9: 551.
19. Rahimi-Madiseh M, Lorigoini Z, Zamani-Gharaghoshi H, Rafieian-Kopaei M. Berberis vulgaris: specifications and traditional uses. Iran J Basic Med Sci 2017; 20: 569–587.
20. Hajhashemi V, Fahmideh F, Ghanadian M. Antinociceptive effect of methanolic extract and alkaloid fractions of Berberis integerrima root in animal models. Avicenna J Phytomed 2018; 8: 227–236.
21. Potdar D, Hirwani RR, Dhulap S. Phyto-chemical and pharmacological applications of Berberis aristata. Fitoterapia 2012; 83: 817–830.
22. Shabbir ASA, Shahzad MSM, Arfat YAY, Ali LAL, Aziz RS, Murtaza GMG, Waqar SA, Alamgeer A. Berberis lycium royle: a review of its traditional uses, phytochemistry and pharmacology. African J Pharm Pharmacol 2012; 6: 2346–2353.
23. Alamgeer, Chabert P, Akhtar MS, Jabeen Q, Delecolle J, Heintz D, Garo E, Hamburger M, Auger C, Lugnier C, et al Endothelium-independent vasorelaxant effect of a Berberis orthobotrys root extract via inhibition of phosphodiesterases in the porcine coronary artery. Phytomedicine 2016; 23: 793–799. https://www.sciencedirect.com/science/article/pii/S0944711316300411.
24. Khan S, Nazir M, Saleem H, Raiz N, Saleem M, Anjum SMM, Zengin G, Mukhtar M, Tousif MI, Mahomoodally FM, et al Valorization of the antioxidant, enzyme inhibition and phytochemical propensities of Berberis calliobotrys Bien. ex Koehne: A multifunctional approach to probe for bioactive natural products. Ind Crops Prod 2019; 141:111693. https://www.sciencedirect.com/science/article/pii/S0926669019307034.
25. Hadi A, Arab A, Ghaedi E, Rafie N, Miraghajani M, Kafeshani M. Barberry (Berberis vulgaris L.) is a safe approach for management of lipid parameters: A systematic review and meta-analysis of randomized controlled trials. Complement Ther Med 2019; 43: 117–124.
26. Tahmasebi L, Zakerkish M, Golfakhrabadi F, Namjoyan F. Randomised clinical trial of Berberis vulgaris root extract on glycemic and lipid parameters in type 2 diabetes mellitus patients. Eur J Integr Med 2019; 32: 100998.
27. Mohammdadi SMA-R, Mosavi SAA-M. Effect of aqueous Berberis integerrima extract on fatty liver and triglyceridemia. J Shahid Sadoughi Univ Med Sci Heal Serv 2019; 27: 1141–1149.
28. Afsharinasab M, Mohammad-Sadeghipour M, Reza Hajizadeh M, Khoshdel A, Mirzaiey V, Mahmoodi M. The effect of hydroalcoholic Berberis integerrima fruits extract on the lipid profile, antioxidant parameters and liver and kidney function tests in patients with nonalcoholic fatty liver disease. Saudi J Biol Sci 2020; 27: 2031–2037.
29. Aryaeian N, Sedehi SK, Khorshidi M, Zarezadeh M, Hosseini A, Shahram F. Effects of hydroalcoholic extract of Berberis integerrima on the anthropometric indices and metabolic profile in active rheumatoid arthritis patients. Complement Ther Med 2020; 50: 102331.
30. Sharma RK, Sharma B, Jindal M, Gupta AK, Kunwar R, Lata S, Yadav AK. Evaluation of hypolipidemic effect of stem part of Berberis aristata in type 2 diabetes mellitus patients as add on therapy. Natl J Physiol Pharm Pharmacol 2017; 7: 1159–1169.
31. Cai Y, Yang Q, Yu Y, Yang F, Bai R, Fan X. Efficacy and underlying mechanisms of berberine against lipid metabolic diseases: a review. Front Pharmacol 2023; 14. https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2023.1283784.
32. García-Muñoz AM, Victoria-Montesinos D, Ballester P, Cerdá B, Zafrilla P. A descriptive review of the antioxidant effects and mechanisms of action of berberine and silymarin. Molecules 2024.
33. Mushtaq Z, Imran M, Saeed F, Imran A, Ali SW, Shahbaz M, Alsagaby SA, Guerrero Sánchez Y, Umar M, Hussain M, et al Berberine: a comprehensive Approach to combat human maladies. Int J Food Prop 2023; 26:

787–807. https://doi.org/10.1080/10942912.2023.2184300.
34. McCarty MF. Nutraceutical and dietary strategies for up-regulating macroautophagy. Int J Mol Sci 2022.
35. Meliani N, Dib MEA, Allali H, Tabti B. Hypoglycaemic effect of Berberis vulgaris L. in normal and streptozotocin-induced diabetic rats. Asian Pac J Trop Biomed 2011; 1: 468–471.
36. Hemmati M, Asghari S, Zohoori E, Karamian M. Hypoglycemic effects of three Iranian edible plants; Jujube, barberry and saffron: Correlation with serum adiponectin level. Pak J Pharm Sci 2015; 28: 2095–2099.
37. Torkamaneh S, Gene-Morales J, Juesas A, Flandez J, Hammami R, Rafieian-Kopaei M, Colado JC. Effects of black Berberis vulgaris L combined with aerobic and resistance exercise on blood metabolic parameters and liver enzymes in obese rats. J Hum Sport Exerc 2021; 16: 18–19.
38. Taheri S, Zarei A, Changizi Ashtiyani S, Rezaei A, Zaheiri S. Evaluation of the effects of hydroalcoholic extract of Berberis vulgaris root on the activity of liver enzymes in male hypercholesterolemic rats. Avicenna J phytomed 2012; 2: 153–161.
39. Neag MA, Bocsan IC, Catinean A, Vesa SC, Balan GG, Parvu M, Muntean DM, Vlase L, Melincovici CS, Pop R, et al Effects of Berberis vulgaris extract on lipid profile, kidney and liver function in experimental dyslipidemia. Rev Chim 2019; 70: 614–618.
40. Ashraf H, Heidari R, Nejati V, Ilkhanipoor M. Effects of aqueous extract of Berberis integerrima root on some physiological parameters in streptozotocin-induced diabetic rats. Iran J Pharm Res 2013; 12: 425–434.
41. Bayani M, Ahmadi-Hamedani M, Jebelli Javan A. Phytochemical and antioxidant activities of Berberis integerrima and Berberis vulgaris and pharmacological effects of the more active species on alloxan-induced diabetic rats. J Med Plants 2016; 15: 111–121.
42. Ghazanfar K, Ahmad B, Akbar S, Younis M, Ahmad M, Masood A. The extracts of Berberis lycium and diabetes mellitus in alloxan monohydrate induced diabetic rats. 2011; 4: 2570–2573.
43. Zaib M, Sharif A, Akhtar B, Khan HM, Akhtar MF, Hassan W, Razzaq F, Nawaz S, Qaisar N. Berberis lycium Royle extracts attenuate inflammation and modulates hyperglycemia in alloxan induced diabetic rats. Pak J Pharm Sci 2020; 33: 1805–1813.
44. Upwar N, Patel R, Waseem N, Kumar Mahobia N. Hypoglycemic effect of methanolic extract of Berberis aristata DC stem on normal and streptozotocin induced diabetic rats. Int J Pharm Pharm Sci 2011; 3: 222–224.
45. Razzaq FA, Khan RA, Feroz Z, Afroz S. Effect of Berberis aristata on lipid profile and coagulation parameters. African J Pharm Pharmacol 2011; 5: 943–947.
46. Alamgeer, Ghuffar A, Ahmad T, Mushtaq MN. Antihyperlipidemic effect of Berberis orthobotrys in hyperlipidemic animal models. Bangladesh J Pharmacol 2014; 9: 377–382.
47. Rasool S, Al Meslmani B, Alajlani M. Determination of hypoglycemic, hypolipidemic and nephroprotective effects of Berberis calliobotrys in alloxan-induced diabetic rats. Molecul 2023.
48. Derosa G, D'Angelo A, Romano D, Maffioli P. Effects of a combination of Berberis aristata, Silybum marianum and monacolin on lipid profile in subjects at low cardiovascular risk; A double-blind, randomized, placebo-controlled trial. Int J Mol Sci 2017; 18: 1–9.
49. Derosa G, Romano D, D'Angelo A, Maffioli P. Berberis aristata/Silybum marianum fixed combination (Berberol®) effects on lipid profile in dyslipidemic patients intolerant to statins at high dosages: A randomized, placebo-controlled, clinical trial. Phytomed 2015; 22: 231–237.
50. Derosa G, D'Angelo A, Maffioli P. The role of a fixed Berberis aristata/Silybum marianum combination in the treatment of type 1 diabetes mellitus. Clin Nutr 2016; 35: 1091–1095.
51. Nannoni G, Alì A, Di Pierro F. Development of a new highly standardized and granulated extract from Monascus purpureus with a high content of monacolin K and KA and free of inactive secondary monacolins and citrinin. Nutrafoods 2015; 14:197–205. Available from: https://doi.org/10.1007/s13749-015-0047-4.
52. Di Pierro F, Putignano P, Ferrara T, Raiola C, Rapacioli G, Villanova N. Retrospective analysis of the effects of a highly standardized mixture of Berberis aristata, Silybum marianum, and monacolins K and KA in patients with dyslipidemia. Clin Pharmacol 2017; 9: 1–7.
53. Di Pierro F, Putignano P, Villanova N. Retrospective analysis of the effects of a highly standardized mixture of Berberis aristata, Silybum marianum, and monacolins K and KA in diabetic patients with dyslipidemia. Acta Biomed 2017; 88: 462–469.
54. Derosa G, Gaudio G, D'Angelo A, Maffioli P. Efficacy of Berberis aristata compared to metformin in improving glycemic control and insulin resistance in patients with type 2 diabetes mellitus. J Food Nutr Res 2020; 8: 212–215.
55. Cicero AFG, Fogacci F, Bove M, Giovannini M, Veronesi M, Borghi C. Short-term effects of dry extracts of artichoke Berberis in hypercholesterolemic patients without cardiovascular disease. Am J Cardiol 2019; 123: 588–591.
56. Trimarco B, Benvenuti C, Rozza F, Cimmino CS, Giudice R, Crispo S. Clinical evidence of efficacy of red yeast rice and berberine in a large controlled study versus diet. Med J Nutrition Metab 2011; 4: 133–139.
57. Marazzi G, Cacciotti L, Pelliccia F, Iaia L, Volterrani M, Caminiti G, Sposato B, Massaro R, Grieco F, Rosano G. Long-term effects of nutraceuticals (berberine, red yeast rice, policosanol) in elderly hypercholesterolemic patients. Adv Ther 2011; 28: 1105–1113.
58. Pisciotta L, Bellocchio A, Bertolini S. Nutraceutical pill containing berberine versus ezetimibe on plasma lipid

pattern in hypercholesterolemic subjects and its additive effect in patients with familial hypercholesterolemia on stable cholesterol-lowering treatment. Lipids Health Dis 2012; 11: 123.

59. *Pirro M, Mannarino MR, Bianconi V, Simental-Mendía LE, Bagaglia F, Mannarino E, Sahebkar A. The effects of a nutraceutical combination on plasma lipids and glucose: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2016; 110: 76–88.*
60. *De Castro-Orós I, Solà R, Valls RM, Brea A, Mozas P, Puzo J, Pocoví M. Genetic variants of LDLR and PCSK9 associated with variations in response to antihypercholesterolemic effects of Armolipid Plus with Berberine. PLoS One 2016; 11: e0150785.*