

REVIEW ARTICLE OPEN ACCESS

Therapeutic Potential of *Berberis vulgaris* in Modulating Metabolic Syndrome Biomarkers: Mechanistic Insights and Functional Food Implications

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ABSTRACT

Barberry (*Berberis vulgaris*) has emerged as a promising functional food candidate for the management of metabolic syndrome due to its diverse bioactive constituents, particularly berberine. This review synthesizes current experimental and clinical evidence regarding its effects on glycemic control, lipid metabolism, blood pressure regulation, and obesity-related parameters. Mechanistic insights indicate that barberry improves insulin sensitivity, enhances glucose uptake, suppresses hepatic gluconeogenesis, modulates lipid metabolism, and exerts antioxidant and anti-inflammatory effects. Clinical findings suggest potential benefits in lowering fasting blood glucose, triglycerides, low-density lipoprotein cholesterol, blood pressure, and central adiposity. In addition, synergistic interactions among alkaloids, flavonoids, and carotenoids may contribute to its multifunctional therapeutic profile. Despite these promising outcomes, evidence remains heterogeneous, and rigorously designed, large-scale randomized controlled trials are required to establish standardized dosing regimens, confirm long-term safety, and support evidence-based clinical integration.

1 | Introduction

Growing scientific and clinical interest has focused on the potential role of complementary and alternative therapies in managing a wide range of health conditions. Historically, medic-

inal plants and herbs have been employed for thousands of years due to their rich composition of bioactive compounds and their associated therapeutic effects. (Marrelli 2021). Within this context, barberry (*Berberis vulgaris*) has emerged as a promising medicinal plant owing to its diverse bioactive constituents,

Abbreviations: ABTS, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid); AMPK, AMP-activated protein kinase; ApoA-II, apolipoprotein A-II; ApoA-III, apolipoprotein A-III; ApoB100, apolipoprotein B100; ApoB48, apolipoprotein B48; BMI, body mass index; BP, blood pressure; BVAE, *Berberis vulgaris* aqueous extract; BVPE, *Berberis vulgaris* polysaccharide extract; CM, chylomicron; CRP, C-reactive protein; CVD, cardiovascular diseases; DALYs, disability-adjusted life years; DPPH, 2,2-diphenyl-1-picrylhydrazyl; FBS, fasting blood sugar; FRAP, ferric reducing antioxidant power; HDL, high-density lipoprotein; HO-1, heme oxygenase-1; HTG, hypertriglyceridemia; Keap1, Kelch-like ECH-associated protein 1; LDL, low-density lipoprotein; LMIC, low- and middle-income countries; LOX, lipoxygenase; MCF-7, Michigan Cancer Foundation-7; MetS, metabolic syndrome; MFCS, multifactorial chylomicronemia syndrome; MTTP, microsomal triglyceride transfer protein; NAC, N-acetylcysteine; Nrf2, nuclear factor erythroid 2-related factor 2; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9; RA, rheumatoid arthritis; RBP4, retinol-binding protein 4; ROS, reactive oxygen species; SBP, systolic blood pressure; SNAP, sodium nitroprusside; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein; WHO, World Health Organization; β -cells, beta cells.

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which may contribute to overall health benefits while generally presenting fewer adverse effects than synthetic pharmacological agents. *Berberis vulgaris*, belonging to the Berberidaceae family, is widely distributed worldwide, particularly in Southern Khorasan (Iran), and is extensively cultivated across Asia and Europe (Moradinezhad et al. 2025). *B. vulgaris* is a woody shrub with diverse anatomical characteristics, native primarily to Central Asia. Berberine is a primary bioactive compound found in the roots, stems, bark, and rhizomes of several plants, including the Oregon grape (*B. aquifolium*) and the Huanglian (*Coptis chinensis*) (Imenshahidi and Hosseinzadeh 2020). The high concentration of berberine (a quinoline alkaloid) in the fruit and root of barberries has been primarily responsible for its many biological properties (Marcinčáková et al. 2025). Berberine has demonstrated glucose-lowering effects comparable to metformin in some experimental and clinical studies. While berberine is also effective at lower concentrations, it reduces lipid accumulation more effectively than metformin. In synergy, it enhanced the effectiveness of metformin (Khorzoughi et al. 2019).

A group of metabolic abnormalities collectively known as metabolic syndrome (MetS) has been linked to adverse health consequences. This definition states that the condition is defined as follows: minimum three out of five risk factors: central obesity, high TG, low HDL cholesterol, high blood pressure (BP) ($\geq 130/85$ mmHg), and impaired fasting glucose (≥ 100 mg/dL) (Venturi et al. 2023). The MetS denotes an individual's heightened susceptibility to developing cardiovascular disease (CVD) and Type 2 diabetes mellitus (T2DM) in the future. Effective implementation of evidence-based strategies for managing metabolic syndrome (MetS) can mitigate associated health risks and improve overall clinical outcomes. Barberry has been shown to improve selected metabolic markers in randomized controlled trials (Nilsson et al. 2019).

The metabolic condition known as T2DM is characterized by hyperglycemia, resulting from inadequate insulin secretion and impaired insulin sensitivity. Individuals with diabetes face an increased vulnerability to progressive major, potentially fatal illnesses, leading to an increase in medical expenses, diminished quality of life, and elevated mortality rates. Over 590 million individuals are expected to have T2DM by 2035, and over the next 10 years, the overall number of fatalities from diabetes is expected to increase by over 50%. Despite the existence of effective medications for managing and treating T2DM, the search for affordable, low-adverse-effect medications remains a significant challenge. Barberry, in particular, has attracted considerable interest in both consumer and scientific communities for its potential (Lazavi et al. 2018).

Globally, there is an increasing prevalence of metabolic illnesses, including diabetes mellitus. On the other hand, less is known about the recent approaches to managing diabetes mellitus and other metabolic disorders (Khashayar et al. 2021). Diabetes mellitus and CVD are essential factors of MetS, placing a considerable burden on the healthcare system. The extent of MetS is estimated to be growing over time. The foundation of managing MetS focuses on improving lifestyle factors, encompassing dietary modifications, weight reduction, and adherence to recommended physical activity levels (Martemucci et al. 2024). CVDs remain the leading cause of mortality globally and are closely linked with

MetS components, including hypertension, dyslipidemia, and central obesity. By 2050, the global incidence of CVDs is projected to increase substantially. Forecasts show that the prevalence of CVD will rise by 90.0%, overall mortality will increase by 73.4%, and disability-adjusted life years (DALYs) will rise by 54.7%. According to recent projections, CVDs will cause 35.6 million deaths by 2050, up from 20.5 million in 2025 (Chong et al. 2024). This number is expected to increase, particularly in developing countries, imposing notable financial pressure on healthcare systems and economies.

Various factors, including obesity, smoking, hypertension, and dyslipidemia, collectively make for the primary causes of CVDs (Roth et al. 2020). Dyslipidemia, a health condition associated with unusually increased plasma lipid levels, including increased total cholesterol (TC), TG, and LDL-C, or decreased HDL-C, has become the prominent modifiable risk factor for CVDs as smoking rates lessen. While hypolipidemic medications are extensively used due to their effectiveness in reducing serum cholesterol levels, their effectiveness is restricted by adverse side effects, including myopathy and hepatotoxicity (Mach et al. 2020; Thompson et al. 2016). In response to these implications, researchers continue to discover natural substances with lipid-modifying properties, particularly within herbal medicine. Many herbs and their derivatives, such as artichokes, cumin, and ginger, have been recognized as potential agents for the treatment of dyslipidemia. Barberry has emerged as a theme of growing scientific interest in this context, attracting attention from both scientific and consumer communities. A key component of CVD prevention is dietary modification, particularly given the growing evidence of a substantial negative correlation among MetS, plant-based bioactives, and CVD risk (Hadi et al. 2019).

Hypertension is a critical health concern worldwide, presenting significant morbidity and mortality rates. Hypertension, often referred to as elevated BP, is a crucial factor in CVDs, including heart attacks, strokes, and heart failure. It imposes a substantial burden on healthcare systems due to its high prevalence and related issues. Management strategies for hypertension typically involve lifestyle changes and pharmacological modifications aimed at lowering BP levels to lessen the risk of CVDs and other associated complications. Barberry, known for its high content of berberine and anthocyanins, has been evaluated for potential cardiovascular benefits. Preliminary research suggests that barberry may positively affect BP, lipid profiles, and cardiovascular health. Some studies suggest that barberry consumption may reduce fasting blood glucose levels and improve vascular function in patients with T2D. In addition, barberry's anti-inflammatory properties and antioxidants may facilitate its cardioprotective effects (Emamat et al. 2020).

Barberry offers several potential health benefits, including hypotensive, anti-inflammatory, and antioxidant properties. Key ingredients in barberry, such as malic acid, oxyacanthine, palmarine, berberine, and berbamine, contribute to its therapeutic effects. It acts as a lipid-lowering agent and exhibits antibacterial, anti-inflammatory, anticarcinogenic, antihistaminic, antihyperglycemic, and antioxidant properties (Hadi et al. 2019; Özgen et al. 2012). The documented glucose- and cholesterol-lowering, and anti-inflammatory effects of berberine have drawn considerable attention to its therapeutic benefits in humans. Berberine's car-

dioprotective properties, as well as barberry's ability to reduce the risk of obesity, have been demonstrated (Cao and Su 2019). The high content of berberine and anthocyanins in barberry, as well as its effects on cardiovascular risk factors, has been extensively studied. However, clinical trials regarding the effects of barberry on cardiometabolic parameters are scarce. Interestingly, giving people with Type 2 diabetes 200 mL of barberry juice improved their blood lipid levels, fasting blood glucose levels, and systolic and diastolic BP.

Furthermore, a study reported that diabetic patients who received 3 g of extract daily for 3 months showed improvements in serum lipids, lipoprotein profile, glucose concentrations, and total antioxidant capacity. Despite these promising findings, previous research on the impact of barberries on cardiovascular risk elements, especially exceptionally high BP, has encountered several constraints. Extensive research has been conducted on the influence of barberry on lipid profile, inflammatory responses, and BP. Studies have shown that barberry extract, administered at doses of 25 and 100 mg/kg body weight, effectively reduces lipoprotein levels, triglycerides (TG), lipid oxidation, and fasting blood sugar (FBS).

In addition, barberry extract demonstrates promising antihypertensive effects. Although some clinical studies have assessed its impact on plasma lipid levels and inflammatory markers, the results have been inconsistent (Emamat et al. 2020). For instance, a study administering 10 g of dried barberry over 8 weeks showed a significant reduction in plasma C-reactive protein (CRP) among individuals with MetS, though only modest changes in low-density lipoprotein cholesterol (LDL-C) were observed (Emamat et al. 2022). Despite growing research interest, previous reviews have not comprehensively synthesized the multifaceted effects of barberry's bioactive compounds, such as berberine and anthocyanins, across the spectrum of MetS components.

Although related species such as *B. integerrima* and *B. aristata* exhibit similar phytochemical profiles, this review primarily focuses on *B. vulgaris* and highlights relevant distinctions. While several clinical studies have evaluated other *Berberis* species (e.g., *B. integerrima*), mechanistic extrapolations to *B. vulgaris* should be interpreted with caution, given phytochemical variability across species. This review uniquely integrates evidence on barberry's impact on glycemic control, lipid metabolism, hypertension, and obesity, while also identifying gaps in current clinical knowledge, thus offering a consolidated and updated perspective for future translational and clinical studies.

2 | Nutritional and Phytochemical Composition of Barberry

The large amounts of vitamins, polyphenols, β -carotene, and minerals (as much as 425.4 mg/100 g of potassium and as much as 51.2 mg/100 g of calcium) present in barberry fruits and the large amounts of vitamins C, P, and E, polyphenols, β -carotene, potassium (over 598.0 mg/100 g), and calcium (over 137.8 mg/100 g) present enable them to be termed as micronutrient-rich crops. The nutritional value of barberry includes energy 69.25 kcal, carbohydrates 16.88%–24.87% NFE, protein 0.50%–1.53%, fat 0.33%–

2.97%, and fiber 2.64%–12.11% (Batoool et al. 2021; Moradinezhad et al. 2025). Barberry (*B. vulgaris*) contains a broad spectrum of bioactive compounds and is rich in phytochemicals. These molecules are beneficial across the food, health, and pharmaceutical sectors. The anthocyanin compounds that provide barberry with color and antioxidant properties are abundant in these fruits (Safari-Khozani et al. 2025; Şensu et al. 2021). Co-pigmentation can reinforce these molecules with other phenolic compounds; however, processing and storage conditions can affect them (Farhadi Chitgar et al. 2018). Anthocyanins, such as delphinidin-3-glucoside and cyanidin-3-glucoside, support the antioxidant property of barberry fruit, but they are liable to in vitro digestion. The extraction of anthocyanins from barberry is influenced by processing and extraction conditions.

Barberries contain a high concentration of phenolic compounds, including gallic acid, caffeic acid, p-coumaric acid, and chlorogenic acid. These phenolic compounds help reduce inflammation, support blood glucose regulation, and mitigate oxidative stress. These components, which support its antioxidant activity, are widespread across distinct barberry genotypes (Gholizadeh-Moghadam et al. 2019). The flavonoids, such as quercetin, apigenin, and rutin, provide additional antioxidant properties to barberry. The total flavonoid content varies across barberry genotypes (Okatan and Çolak 2019). One of the primary alkaloids present in barberry is berberine. Its anti-inflammatory, antibacterial, antifungal, insulin-resistance-improving, anti-cancer, and antioxidant properties are among its many therapeutic applications. The alkaloid components are present in various plant parts, including stems, roots, bark, and rhizomes (Moravcová et al. 2025). Palmatine and berbamine are other significant alkaloids, which facilitate its therapeutic use. Protoberberine is also widely researched for its pharmacological uses. The antioxidant qualities of barberry fruit are mainly due to carotenoids (Table 1). In addition, these substances are liable to digestive processes (Şensu et al. 2021).

3 | Potential Application of Barberry in the Food Industry

Barberries are widely used in the food industry for their delicious taste and color. It has been traditionally consumed as a fruit and as a medicinal remedy and is increasingly used as a functional food ingredient. It is widely used in Persian cooking to prepare sauces, chocolates, and jams. In traditional medicine, it is widely used in many pharmacological and biological activities (Sun et al. 2021). The fruit powder can be used in the food industry to fortify snack products, such as puffed corn snacks. Its addition increases vitamin C, dietary fiber, and anthocyanin content while reducing oil content and lipid oxidation during storage. Barberries decrease acidity and peroxide levels, enhancing product stability in food matrices during storage. In addition, it enhances nutritional quality and consumer acceptance when used at optimal levels, making it a desirable functional ingredient for innovative food products (Bakmohamadpor et al. 2021).

Barberry is used as a functional ingredient to enhance the nutritional profile of food products, thanks to its high levels of vitamins, minerals, fiber, and bioactive compounds. It is incorporated into products such as confectionery, beverages, and

TABLE 1 | Major bioactive compounds in *Berberis vulgaris* and biological relevance.

Compound	Chemical class	Main biological relevance	Relative abundance ^a	References
Berberine	Isoquinoline alkaloid	Antioxidant, anticancer, anti-inflammatory, antibacterial, antifungal	High	Ciorîță et al. (2024), Karimkhani et al. (2019), Och et al. (2023)
Anthocyanins	Flavonoid (polyphenolic compound)	Antioxidant, anti-inflammatory	High	Şensu et al. (2021)
Carotenoids	Terpenoid (C40 tetraterpenoid)	Antioxidant	Medium	Rahimi-Madiseh et al. (2017), Şensu et al. (2021)
Berbamine	Bisbenzylisoquinoline alkaloid	Anti-inflammatory, immunomodulatory	Low	Ciorîță et al. (2024)
Palmatine	Protoberberine alkaloid	Antioxidant	Medium	Ciorîță et al. (2024)

^aRelative abundance estimated based on reported phytochemical profiling studies.

snack foods to provide natural color and antioxidant qualities. Barberry also enhances sensory qualities by imparting a distinctive flavor and acidity. Its bioactive compounds also support the development of functional and health-oriented food products (Naji-Tabasi et al. 2021). Lactic acid bacteria fermentation has been used to improve the bioactive and functional properties of barberry root. Microbial biotransformation increases the release of berberine and enhances its antioxidant, antibacterial, and antidiabetic properties. These results support the use of fermented barberry root extract in functional food products that provide additional health benefits (Amini et al. 2025). Due to its contribution to phenolic compound production, it has potential applications in the food industry. Barberries can be used as a natural bioactive ingredient in food compositions, even if their antioxidant potential may differ from that of other native fruits. It enhances the nutritional value and sensory appeal of food by adding organic acids, phytochemicals, and a unique flavor. Barberry, therefore, represents a potential candidate for incorporation in traditional products, functional meals, and health-conscious culinary applications (Khadivi et al. 2024).

4 | Mechanism of Action of Barberry

4.1 | Antidiabetic Effects

The WHO has designated diabetes mellitus as one of the four primary non-communicable diseases requiring immediate attention from all stakeholders. It ranks as the third primary risk factor for premature mortality worldwide due to hyperglycemia. Both common forms of diabetes can result in multisystem complications affecting both macrovascular and microvascular endpoints. Retinopathy, nephropathy, and neuropathy are examples of microvascular problems; macrovascular complications encompass stroke, peripheral vascular disease, and ischemic heart disease (Abd El-Wahab et al. 2013). Diabetes mellitus is among the most prevalent metabolic disorders worldwide; it is primarily caused by two factors: reduced insulin sensitivity in insulin-sensitive tissues and decreased insulin production by pancreatic β -cells. The molecular processes underlying insulin metabolism and their relationship to CVD are essential to the pathogenesis of T2DM. The global prevalence of T2DM is primarily attributable to risk factors including obesity, lifestyle choices, genetic predisposition, gut dysbiosis, epigenetic changes, and mitochondrial dysfunction. Diabetes is currently the sixth most common disease in terms of DALYs. Based on data, statistical estimates suggest that by 2030, there may be 7079 cases of diabetes per 100,000 people worldwide (Khan et al. 2020).

Barberries are well-known for their antidiabetic effects. It has been demonstrated that the active ingredients in barberry, such as berberine, improve insulin sensitivity and reduce insulin resistance, thereby producing hypoglycemic effects. Compared with the placebo group, individuals taking 1000 mg of barberry daily may have improved fasting blood glucose and HDL-C, as well as TG, LDL-C, and TC levels. To improve glycemic management, barberry may enhance glucose metabolism and reduce insulin resistance. The specific mechanism may involve activation of AMP-activated protein kinase (AMPK), an enzyme crucial for regulating cellular glucose uptake and metabolism. In patients with impaired beta-cell function, berberine may improve insulin

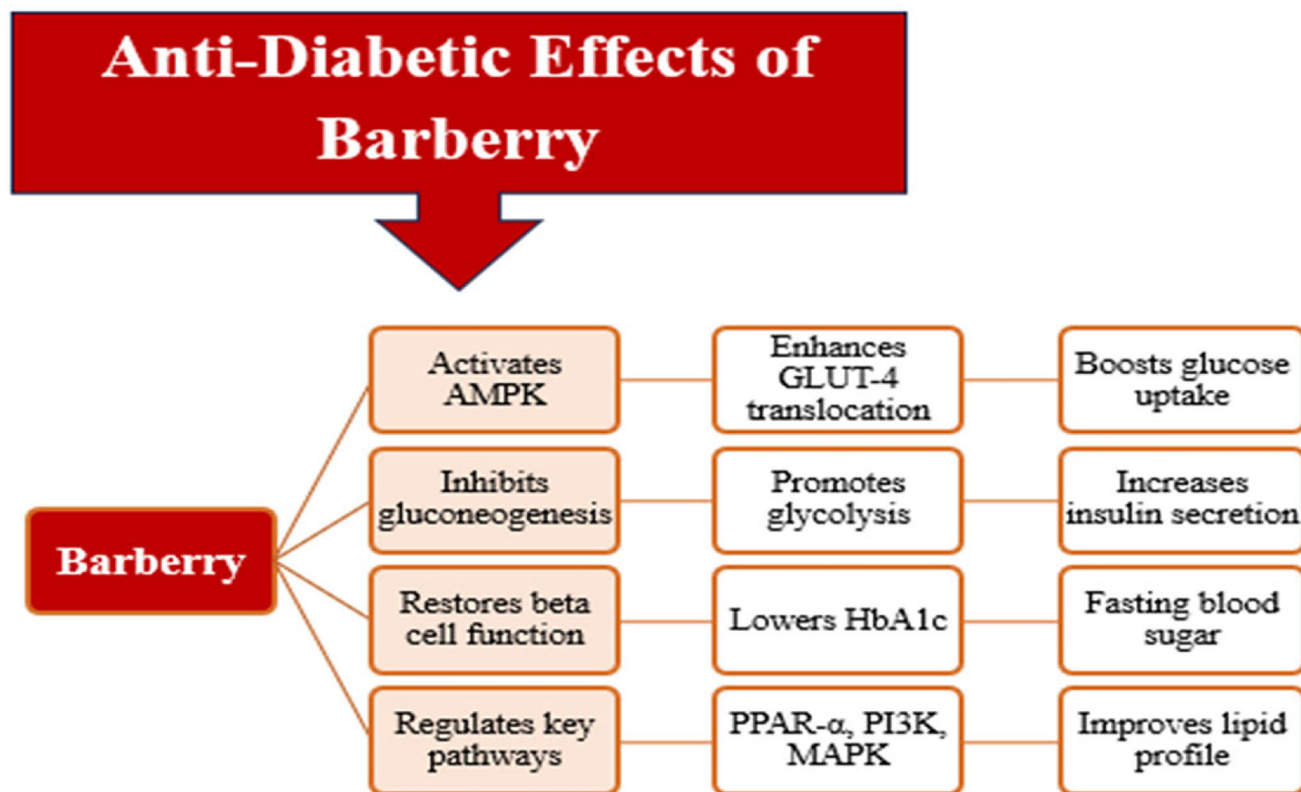


FIGURE 1 | The mechanism of the antidiabetic action of barberry.

secretion by restoring beta-cell function. Alpha-glucosidase inhibitory effects may be attributable to barberry, given its functional similarity to insulin. Berberine's cholesterol-lowering effect also mitigates the cardiovascular consequences of diabetes. Random blood glucose and fasting blood sugar decreased significantly after a month of berberine use (Rashidi et al. 2018). Barberry extracts may inhibit α -glucosidase activity, thereby attenuating postprandial glucose excursions. They may also regulate hepatic enzymes, thereby reducing glycated hemoglobin levels in patients with diabetes (Montazerifar et al. 2023). Berberine alters glucose metabolism by promoting glycolysis, increasing glucokinase activity, increasing insulin secretion, and inhibiting hepatic gluconeogenesis and adipogenesis. In patients with diabetes, berberine effectively reduces hemoglobin A1c (HbA1c). Berberine regulates peroxisome proliferator-activated receptor- α (PPAR- α), protein kinase C (PKC), mitogen-activated protein kinase (MAPK), adenosine monophosphate-activated protein kinase (AMPK), and PPAR effectors. Phosphatidylinositol 3-kinase (PI3K) suppression in diabetes can alter the efficiency with which insulin activates or regulates glucose transporters 1 and 4 (GLUT-1 and GLUT-4). GLUT-4 translocation in cells increases glucose uptake and reduces blood glucose levels (Figure 1) (Sudhakar et al. 2021).

4.2 | Antihypertensive Effects of Barberry

When BP against arterial walls exceeds 140/90 mmHg, it is known as hypertension, or high BP. Although common, if left untreated, it can lead to significant health complications. People

with high BP frequently do not exhibit any symptoms. Regular BP measurements are essential for managing hypertension and detecting it early (Petersen et al. 2020). BP monitoring reduces the risk of related health problems and facilitates prompt management. Since cardiovascular illnesses and early mortality are mainly caused by hypertension, it presents a significant threat to world health (Unger et al. 2020). Over the past few decades, the global mean BP has stabilized or slightly reduced despite consuming BP-lowering drugs. Ironically, the occurrence of hypertension increased, especially in low- and middle-income countries (LMICs). An estimated 1.4 billion persons, or one-third of all adults, suffer from hypertension. In 2019, CVD was the cause of over one-third (18.6 million) of these deaths. Elevated BP, also known as hypertension, is the primary risk factor, contributing to 9.3% of DALY lost worldwide and 10.8 million deaths, 19.2% of all deaths in 2019. The effects of elevated BP are numerous. There is a 35% higher risk of ischemic stroke, a 29% increased risk of myocardial infarction (MI), and a 45% increased risk of abdominal aortic aneurysm for every 20 mmHg increase in systolic BP (SBP) (Schutte et al. 2021).

Different risk factors, such as excessive salt consumption, low potassium intake, obesity, increased alcohol use, physical inactivity, and poor dietary choices, can be reasons for the variations in the incidence of hypertension among different locations (Mills et al. 2020). Through various mechanisms, berberine reduces vascular resistance and acts as a vasodilator, lowering BP. It lowers BP by promoting endothelial relaxation, stimulating nitric oxide release, and modulating the central nervous system (Lazavi et al. 2018).

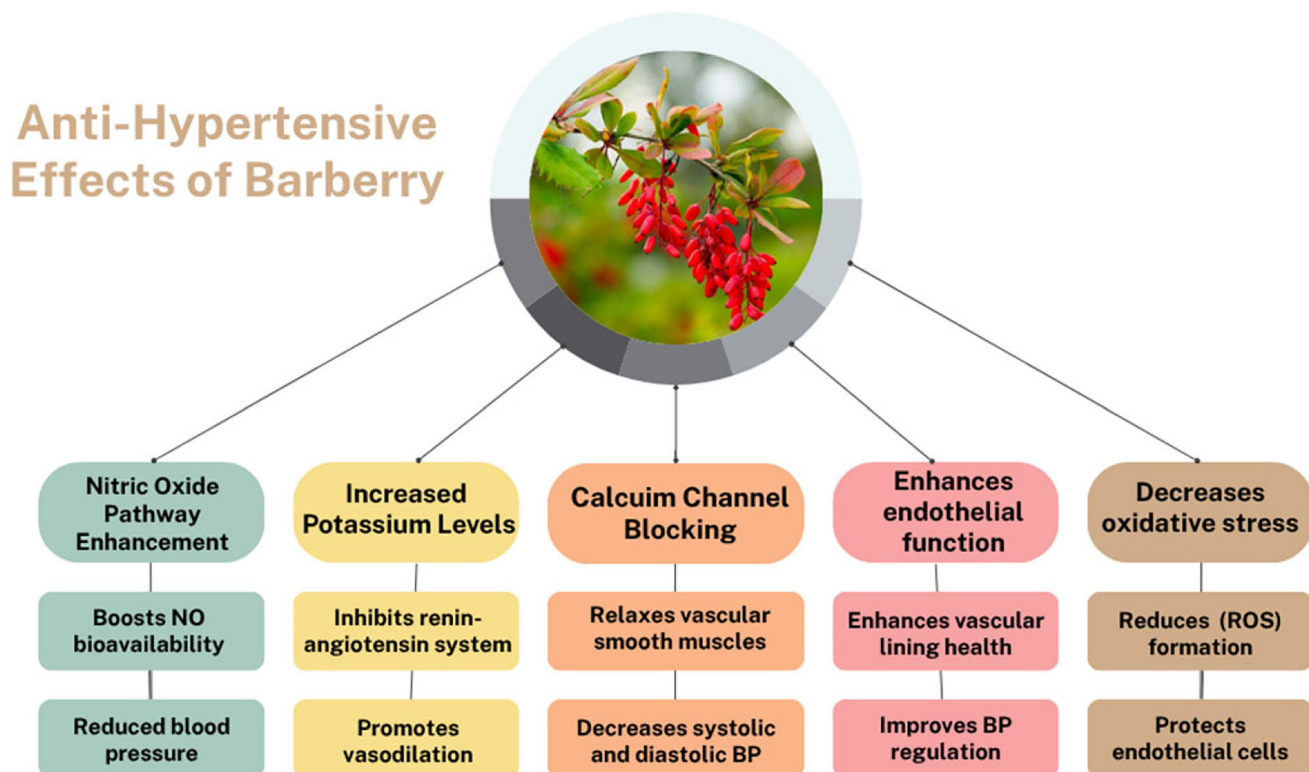


FIGURE 2 | The mechanism of antihypertensive action of barberry.

Barberry root is used to treat metabolic disorders, particularly hypertension. Reductions in SBP and diastolic blood pressure were observed. These findings suggest that barberry root may exert antihypertensive effects in this population. It blocks muscle calcium channels, reducing BP, and also increases potassium, thereby inhibiting the renin-angiotensin pathway (Kamyab et al. 2020). Barberry fruit extract has been shown to reduce hypertension by lowering left ventricular systolic pressure and ventricular hypertrophy, while decreasing medial wall thickness (Mahdavi et al. 2016).

Berberine, an active ingredient in barberry root with known hypotensive properties, is present in the root. Berberine may exert an antihypertensive effect by improving endothelial function, reducing oxidative stress, and regulating nitric oxide pathways. Supplementing with barberry root may lower BP, potentially via enhanced vascular endothelial function and increased nitric oxide bioavailability (Rostami et al. 2023; Venturi et al. 2023) (Figure 2).

4.3 | Barberry Effects in Lowering Obesity

The imbalance between the energy consumed and the energy obtained from food is the etiology of obesity. The extra energy consumed, especially carbohydrates, is stored as fat, which can increase fat cell size or number (Oussaada et al. 2019). The pathological lesions of obesity are fat cell hyperplasia and hypertrophy. Enlarged fat cells release free fatty acids and peptides, which are the primary reasons for the clinical issues associated with obesity. Other illnesses, including gallbladder disease, heart disease,

osteoarthritis, diabetes mellitus, and some types of cancer, are the result of these two processes. There are many different types of medical, social, and psychological disability. The effects of excess weight on mortality and morbidity have been recognized for over 1000 years (Sørensen et al. 2022).

In 1997, the WHO admitted obesity to be a serious worldwide epidemic and public health hazard. BMIs of 25 kg/m² or more are generally considered overweight, and those of 30 kg/m² or higher are considered obese. The WHO estimates that over 1.9 billion individuals who are 18 years of age or older are overweight, and over 650 million of those individuals are obese. Over the previous four decades, obesity has become much more commonplace worldwide. If current trends continue, by 2030, most adults will either be overweight or obese. The major contributor to the worldwide burden of disability is highlighted as obesity, which affects almost all age groups, with serious social and psychological complications (Haththotuwa et al. 2020).

The MetSs are reasons for high mortality and morbidity, which are frequently associated with obesity (Goodarzi et al. 2018). Berberine, the main constituent of barberry, may reduce obesity in several ways. By blocking inflammatory signaling, which reduces pro-inflammatory cytokine levels, a major contributor to inflammation-related obesity, it lessens fat storage and muscle loss. Furthermore, it reduces cellular oxidative stress by inhibiting the production of reactive oxygen species. Barberry is a promising natural treatment for obesity management, as it supports weight and BMI control. Berbamine, a derivative of barberry, has been shown to reduce fat droplet formation in cells. It reduced both the number and size of lipid droplets in

adipocytes. This helps lower the risk of obesity by blocking fat buildup (Emamat et al. 2022; Wang et al. 2016).

Barberry extract effectively reduced obesity-related measures in patients with rheumatoid arthritis (RA) by significantly decreasing waist and hip circumference, body fat percentage, and blood glucose levels compared with the placebo group. In addition, it improves lipid profiles by reducing LDL cholesterol and increasing HDL cholesterol, thereby contributing to better overall metabolic health (Aryaeian et al. 2020). Barberry, particularly its active compound berberine, has been shown to effectively reduce obesity by improving metabolic health. Clinical studies and animal models have shown that berberine reduces body fat percentage and improves lipid profiles by lowering LDL cholesterol and increasing HDL cholesterol. These effects contribute to its overall efficacy in the management of obesity and related metabolic disorders (Khashayar et al. 2021).

4.4 | Anti-Hyperlipidemic Effect of Barberry

Elevated blood lipid levels, resulting from various inherited and acquired conditions, are known as hyperlipidemia. While HDL cholesterol helps regulate cholesterol levels, elevated LDL cholesterol increases the risk of vascular disease and atherosclerotic plaque formation. Treating hyperlipidemia according to each patient's unique risk profile is essential for lowering cardiovascular risk (Kim et al. 2023).

TGs and blood cholesterol levels rise due to alterations in lipoprotein metabolism and transport, a condition known as hyperlipidemia. Very low-density lipoproteins (VLDL), produced in the liver, and chylomicrons (CM), derived from dietary lipids, transport TGs. Insulin, which restricts fatty acid intake and encourages the destruction of ApoB100, as well as the free fatty acids and the enzyme microsomal triglyceride transfer protein (MTTP), all influence VLDL production, which depends on the presence of ApoB100. After forming in the intestines, CMs are packed with MTTP and ApoB48. They also acquire extra apolipoproteins in plasma, which influences their clearance. Elevated amounts of these lipoproteins lead to hyperlipidemia. The interplay between common and uncommon genetic variants and non-genetic factors underlies the complex genetic condition known as hypertriglyceridemia (HTG). Individuals with multiple polygenic influences are more likely to have elevated TG levels, which are often exacerbated by lifestyle choices (Sirwi and Mahmood Hussain 2018; Zilaei et al. 2014).

Unusually asymptomatic until severe HTG or CVD manifests, pure HTG is characterized by increased TG production, raised VLDL levels, and normal LDL levels. Combined hyperlipidemia, which is frequently linked to insulin resistance and the buildup of liver fat, is characterized by elevated ApoB levels and tiny dense LDL particles due to the liver's overproduction of VLDL and poor clearance of ApoB-containing particles. Lipoprotein-related anomalies include aberrant expressions of PCSK9, ApoA-II, and ApoC-III. Insulin resistance in both isolated hyperlipidemia and mixed hyperlipidemia is influenced by visceral obesity. When secondary conditions, such as uncontrolled diabetes or weight gain, aggravate the disease and cause multifactorial chylomicronemia

syndrome (MFCS), severe hyperglycemia can result (Saadatagah et al. 2025).

Barberry, particularly its main constituent, berberine, has several mechanisms that reduce cholesterol. Berberine inhibits HMG-CoA reductase, thereby reducing endogenous cholesterol synthesis. It also modulates intestinal cholesterol absorption pathways (Chang et al. 2012). In addition, it reduces TGs by activating the AMPK pathway, which increases fatty acid oxidation (Zhang et al. 2025). Furthermore, it enhances LDL-C clearance from the bloodstream by upregulating LDL-C receptor expression and downregulating PCSK9 expression. Berberine also prevents fat accumulation by promoting bile acid production and facilitating cholesterol excretion (Dong et al. 2014). Barberry anthocyanin polyphenols increase energy expenditure in muscle and adipose tissues and suppress lipogenic genes (Emamat et al. 2022).

Barberry extracts enhanced overall antioxidant capacity and significantly reduced blood TG. Studies on humans showed that using barberry juice or extract lowered lipid levels and FBS in individuals with diabetes and MetS. These results suggest that barberry has potential as a functional food that can help control hyperlipidemia and protect against heart disease (Figure 3) (Emamat et al. 2022).

4.5 | Barberry Effects in Lowering CVDs

The cardiovascular system consists of the heart and blood vessels. The significant issues that can affect the cardiovascular system are irregularities in the conduction system, MI, and CVDs (Musazadeh et al. 2025):

- Coronary heart disease, also known as coronary artery disease (CAD), is known for causing MI, heart failure, and angina. This is due to reduced myocardial perfusion
- Cerebrovascular disease includes ischemic stroke and related cerebral vascular events
- Peripheral artery disease (PAD) is the name of limb-related vascular disease due to the blockage of an artery in that region (Li and Ma 2023).

CVDs are a significant cause of mortality worldwide, primarily due to atherosclerosis, which is influenced by lifestyle factors like smoking, poor diet, and physical inactivity. The modifiable risk factors together account for the risk of a first MI. These variables include hypertension, excessive smoking, diabetes, psychosocial factors, dyslipidemia, abdominal obesity, poor intake of fruits and vegetables, alcohol use, and physical inactivity. Programs for promoting health include a strong emphasis on quitting smoking, exercising, maintaining a balanced diet, and keeping weight, blood sugar, BP, and cholesterol levels within healthy limits. Age, gender, and family history are examples of non-modifiable risk factors that influence CVD risk. The lifelong risk of heart disease is still significant, especially as people age, even with advancements in therapy (Teo and Rafiq 2021).

The primary reason for mortality worldwide is CVD, which is projected to have claimed 17.8 million lives in 2017. One of the main components of CVD is vascular disease, which is caused

Barberry Mechanism in Reducing Hyperlipidemia

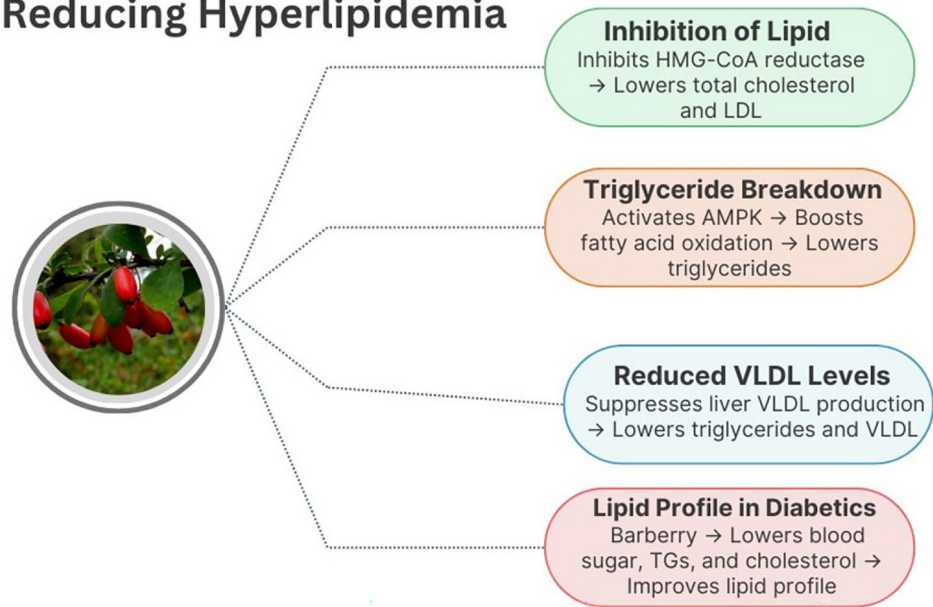


FIGURE 3 | The anti-hyperlipidemic effect of barberry.

by vascular remodeling. Vascular remodeling involves the reorganization of the extracellular matrix and the migration, growth, and death of cells. Even though this mechanism is adaptive for regulating BP, diseases like hypertension and atherosclerosis cause it to become pathological. Influenced by inflammatory cytokines, hemodynamic stimuli, and growth factors, key cell types in the arterial wall, such as vascular smooth muscle cells, fibroblasts, endothelial cells, and swelling cells, contribute to these alterations.

Several findings indicate that *B. vulgaris* consumption may effectively reduce CVD risk factors in patients with any MetS. Berberine modulates cholesterol homeostasis by upregulating hepatic LDL receptor expression and downregulating PCSK9 expression (Rui et al. 2021). A significant reduction in SBP was observed after three weeks of treatment, consistent with earlier studies demonstrating Barberry's antihypertensive and vasodilatory effects. In addition, reductions in waist circumference and TG were observed, thereby improving metabolic health. Clinical trials also reported decreased body weight, TGs, cholesterol, and insulin secretion with barberry supplementation. These effects suggest that barberry may be effective in managing hypertension, obesity, and other CVD risk factors (Lazavi et al. 2018).

5 | Barberry's Potential Adverse Effects

Although barberry is widely used for its therapeutic potential, caution is generally advised regarding its safety and appropriate dosing. It is usually considered safe. However, the active ingredient in barberry, berberine, can cause gastrointestinal symptoms, including vomiting, diarrhea, and nausea, as well as gastric ulcers, at higher doses. In some severe cases, it can also lead to neurological problems, including tremors and

paralysis (Kamrani Rad et al. 2017). Barberries may interact with antidiabetic medications, potentially lowering blood glucose levels. When medication and barberry are used concurrently, it can cause excessive hypoglycemia, posing serious health risks to patients. It can also interact with liver enzymes, affecting the metabolism of other drugs (Fan et al. 2025). While allergic reactions to its consumption are rare, respiratory and skin irritation may occur in individuals allergic to Berberidaceae plants. For elderly individuals or those with pre-existing medical conditions, pregnant women, and breastfeeding women, it is advisable to consume barberry in moderation (Kamrani Rad et al. 2017). These abnormalities are dose-dependent. In humans, barberry extract at doses above 1000 mg/day has not been well studied. At doses above this level, the risk of side effects may increase; further human studies are required to determine safe consumption limits (Bathaei et al. 2025).

6 | Comparison Between *B. vulgaris* Extract and Pure Berberine

The biological effects of pure berberine and extracts from *B. vulgaris* differ significantly in their functions. Although the *B. vulgaris* extract was significantly less active, it exhibited substantial cytotoxicity against MCF-7 cells, with normal cells also being damaged. These extracts exhibited strong antioxidant activity, attributable to several bioactive phytochemicals. Pure berberine exhibits cytotoxicity on its own and requires combination with the nitric oxide donor SNAP to achieve synergistic anticancer effects. Compared with isolated berberine, whole plant extracts demonstrated more substantial and potent biological activity (El Khalki et al. 2018). *B. vulgaris* preparations include Berberine along with several other bioactive compounds that increase overall activity. Pure berberine is a single isoquinoline alkaloid primarily responsible for its antidiabetic effects. Green glycerol

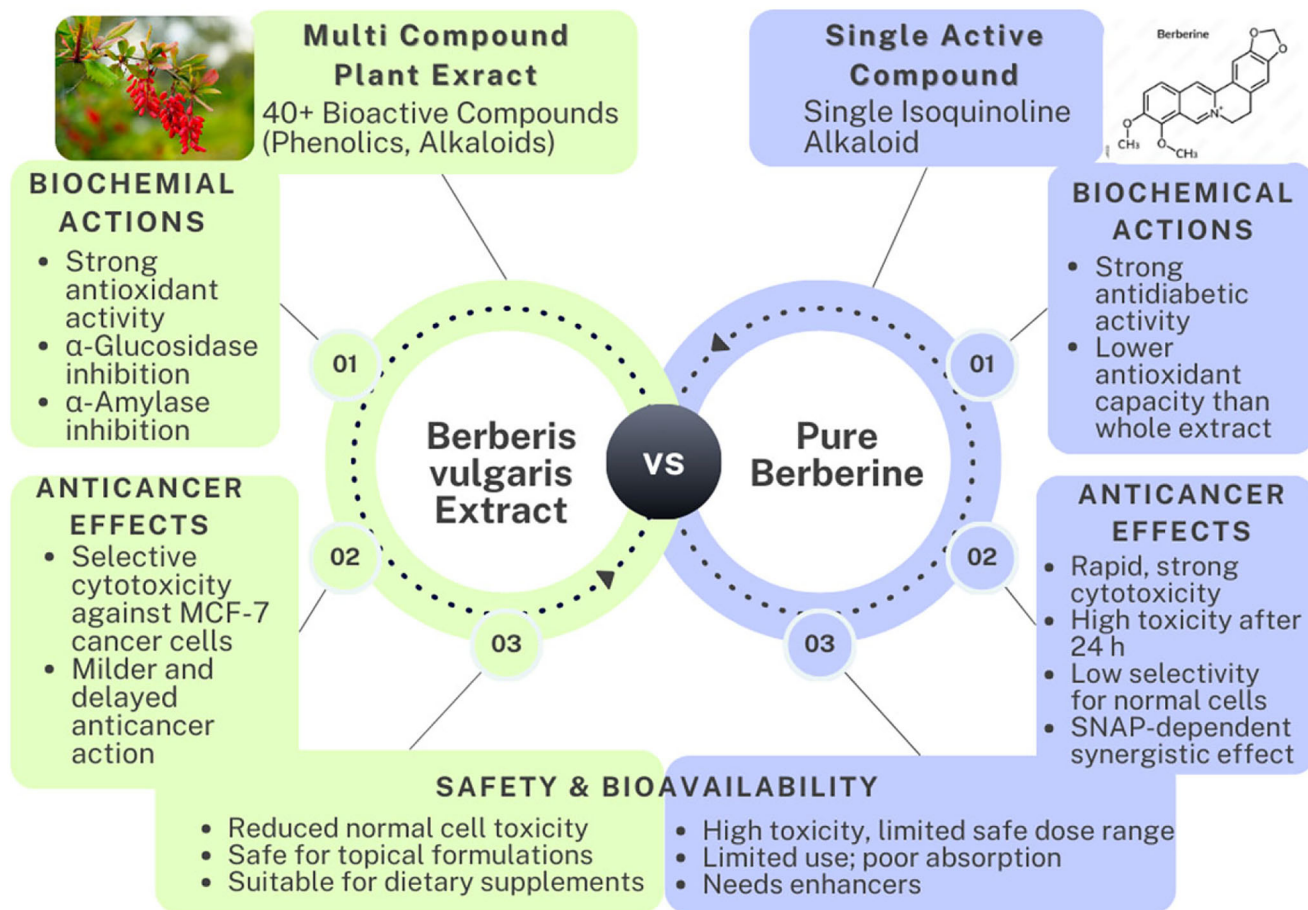


FIGURE 4 | The comparison between *B. vulgaris* extract and pure berberine.

water extracts demonstrated strong anti-inflammatory, anti-melanogenic, and antioxidant properties, not entirely attributable to berberine. Furthermore, the extracts demonstrated strong inhibition of α -glucosidase and α -amylase, indicating a synergistic effect of several components. These extracts, unlike pure berberine, “may be suitable for use in topical preparations and dietary supplements, subject to dose standardization and safety evaluation” (Dulić et al. 2019).

Unlike pure berberine, a single alkaloid, *B. vulgaris* extract contains modest levels of berberine (78.95 $\mu\text{g/g}$) but is rich in a variety of phenolic compounds, including 40 identified bioactive compounds. In contrast to berberine alone, the extract exhibited potent multi-assay antioxidant activity (FRAP, ABTS, DPPH) due to phytochemical synergy. Although pure berberine exhibited more potent and faster anticancer effects, it was highly toxic after 24 h. On the other hand, the plant extract was more selective for cancer cells and caused milder, delayed damage. Only the entire extract showed a distinct relationship between phenolic content, antioxidant activity, and cell survival (Figure 4) (Ivan et al. 2024). *B. vulgaris* root and leaf extracts exhibited broad-spectrum antibacterial and antifungal activity, inhibiting both Gram-positive and Gram-negative microorganisms, in contrast to pure berberine. The hydro-alcoholic extracts demonstrated multi-compound antibacterial activity, being more effective against bacteria than fungi. *Aspergillus* and *Fusarium* species are among the toxic fungi whose mycelial growth was specifically inhibited by root extracts. Strong antioxidant and antibacterial activities

demonstrate the functional qualities of whole-plant extracts, which surpass those of isolated berberine (El-Zahar et al. 2022). A summary of clinical, experimental, and mechanistic studies evaluating the therapeutic effects of *Berberis* species and berberine on metabolic biomarkers is presented in Table 2.

7 | Conclusion

Barberry may represent a promising complementary approach to the management of MetSs, particularly given its high content of bioactive compounds, notably berberine. Barberry demonstrates promising therapeutic potential in modulating biomarkers of MetS through multifaceted mechanisms, including improved insulin sensitivity, lipid regulation, vascular protection, and anti-inflammatory effects. In lipid regulation, it lowers TG and LDL-C levels while raising HDL-C levels. In addition, in BP management, it exhibits notable antihypertensive effects. These physiological improvements collectively support its anti-obesity, antidiabetic, antihypertensive, and anti-hyperlipidemic properties. With further validation, barberry could be formally considered in dietary recommendations or as a complementary therapeutic agent in MetS management frameworks.

8 | Future Perspectives

Future investigations should focus on standardized extract characterization, dose-response evaluation, multi-center randomized

TABLE 2 | Therapeutic effects of *Berberis* species and berberine on metabolic biomarkers.

Plant component	Study designs/ model	Duration	Method/mechanism	Results	Citations
Barberry (root extract)	Placebo vs. barberry extract	3 months	Participants were randomly assigned either barberry root extract (500 mg daily) or a placebo (500 mg of starch powder) in a three-blind randomized clinical trial (RCT).	The intervention group, compared with the placebo group, showed reductions in factors associated with metabolic syndrome (serum lipids, fasting blood glucose, blood pressure, weight, and waist circumference).	Rostami et al. (2023)
Barberry (dried black-purple barberry)	84 patients between the ages of 20 and 65 with a history of hypertension	2 months	Participants were randomly assigned to receive either a placebo or 10 g/day of dried barberry.	Improved lipid profile and inflammatory markers when barberry powder was administered as opposed to a placebo	Emamat et al. (2022)
Barberry juice	46 diabetic patients (30–70 years), 27 women, and 15 men	8 weeks	200 mL of barberry juice was given to diabetic patients. The control group received no intervention.	Significant reductions in FBS, TC, TG, and BP were observed.	Lazavi et al. (2018)
Barberry extract (<i>Berberis integerrima</i>)	70 patients with rheumatoid arthritis	3 months	A sample size of 35 per group. Patients were randomly assigned to intervention or placebo groups. Seventy active RA patients were randomly assigned to receive either six capsules of 500 mg barberry extract or a placebo for 3 months.	Significant improvements were observed in fasting blood glucose, triglycerides, LDL-C, HDL-C, and systolic and diastolic blood pressure.	Aryaeian et al. (2020)
<i>B. vulgaris</i> L. root extract	80 pre-diabetic patients with an age range of 20–65 years	6 weeks	Randomly assigned to intervention and placebo groups. Both groups continued their oral hypoglycemic medication, with either 157.3 mg of berberine and 1000 mg of dry extract or placebo capsules for 6 weeks.	Significant improvements were observed in FBS, fructosamine, and fasting insulin. TC and low-density lipoprotein levels decreased in the intervention group.	Tahmasebi et al. (2019)
<i>B. integerrima</i>	70 patients with T2DM (18–75 years)	8 weeks	Randomly assigned to receive either the extract solution (5 mL twice daily, equivalent to 1000 mg of dry extract) along with standard treatment or only standard treatment (metformin).	The interventional group showed a significant reduction in FBS and serum glycosylated hemoglobin (HbA1c) compared to the control group.	Soltani et al. (2021)

(Continues)

TABLE 2 | (Continued)

Plant component	Study designs/ model	Duration	Method/mechanism	Results	Citations
<i>B. vulgaris</i> fruit extract	Animal study (rats)	6 weeks	Streptozotocin-induced diabetic adult was treated daily with the administration of <i>Berberis vulgaris</i> fruit extract at 3.5% and 7.5% of drinking water.	<i>B. vulgaris</i> fruit extract at a concentration lessened serum and liver lipid peroxidation, while a significant increase in total thiol content was observed in liver and kidney tissues.	Ahmadi et al. (2024)
Leaves, fruits, and stems of <i>B. vulgaris</i>	In vitro models	Not specified	Accelerated solvent extraction (ASE)	Derivative exhibited oxidation inhibitor and LOX inhibitory activity, decreasing intracellular ROS production.	Och et al. (2023)
Berberine BBR	96 adult Wistar rats (aged 8–10 weeks)	14 days	BBR and BBR-loaded micelles were administered to rats for 14 days before inducing stroke. The micelle characteristics and brain inflammatory markers were assessed.	Displayed reduced brain inflammation compared to stroke-only rats (rat nano micelle ischemia model)	Azadi et al. (2021)
<i>B. vulgaris</i> L.	Animal and cell culture models (mice hepatocytes)	Not specified	Co-treatment with berberine and ROS scavenger NAC reversed cholesterol-induced ROS generation and oxidative damage. Activated Keap1/Nrf2/HO-1 pathway, mitigating oxidative imbalance and programmed cell death induced by cholesterol overloading in hepatocytes.	Berberine regulates apoptosis in the liver. Display potential as a therapeutic agent for improving cholesterol overloading that is associated with CVD.	Ye et al. (2022)
<i>B. vulgaris</i> L.	In vitro model	1 month	Tested for anticoagulant and antiplatelet effects on human whole blood	<i>B. vulgaris</i> polysaccharide extract (BVPE) increases coagulation time, indicating potential anticoagulant effects. <i>B. vulgaris</i> aqueous extract BVAE also displayed effective antiplatelet activity, suggesting potential benefits in managing cardiovascular complications associated with metabolic syndromes	Mohd Nor et al. (2019)

controlled trials, and integration of omics-based approaches to clarify molecular signatures associated with metabolic improvements. In addition, food matrix interactions and bioavailability optimization strategies warrant further exploration.

Author Contributions

Fakhar Shahid: conceptualization, data curation, writing – original draft, writing – review and editing. **Ifrah Jabeen:** data curation, writing – original draft, writing – review and editing. **Muhammad Inam-Ur-Raheem:** methodology, data curation, writing – review and editing, supervision. **Amin Mousavi Khaneghah:** writing – original draft, writing – review and editing, supervision. **Muhammad Abid:** writing – review and editing. **Rana Muhammad Aadil:** conceptualization, data curation, writing – original draft, writing – review and editing, supervision.

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The authors declare no conflicts of interest.

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