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REVIEW ARTICLE

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BERBERIS VULGARIS IN THE PREVENTION AND TREATMENT OF METABOLIC DISORDERS: A SYSTEMATIC REVIEW OF ITS ANTI-DIABETIC, ANTI-HYPERTENSIVE, AND ANTI-HYPERLIPIDEMIC EFFECTS

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ABSTRACT: Background: Metabolic disorders such as diabetes, hypertension, and hyperlipidemia represent interconnected global health challenges with escalating prevalence. Despite advances in pharmacotherapy, conventional treatments often fail to address the multifactorial nature of these conditions and pose risks of side effects. *Berberis vulgaris* (barberry), a medicinal plant enriched with berberine and other bioactive compounds, has emerged as a promising alternative due to its multi-targeted therapeutic potential. This review explores the role of *B. vulgaris* in the prevention and treatment of metabolic disorders, highlighting its innovative mechanisms and clinical applicability. **Methods:** A systematic review was conducted to analysed preclinical and clinical studies on *B. vulgaris*. Phytochemical profiling using advanced techniques like HPLC and GC-MS was assessed, along with pharmacological evaluations of its anti-diabetic, anti-hypertensive, and anti-hyperlipidemic properties. Mechanistic pathways, including AMPK activation, RAAS modulation, and HMG-CoA reductase inhibition, were explored. Toxicity studies and emerging formulation strategies, such as nanomedicines and functional foods, were reviewed to evaluate safety and efficacy. **Results:** *B. vulgaris* exhibits potent therapeutic activity by lowering blood glucose, regulating blood pressure, and reducing lipid levels. Recent evidence also highlights its role in gut microbiota modulation, oxidative stress reduction, and anti-inflammatory action, offering a systemic approach to metabolic regulation. Advanced formulations, including barberry-based nutraceuticals, have enhanced bioavailability and therapeutic outcomes in recent studies. **Conclusion:** *Berberis vulgaris* offers an innovative, nature-inspired solution for addressing metabolic disorders. While its potential is evident, further large-scale clinical trials and formulation standardization are imperative to integrate it into mainstream healthcare.

Keywords: *Berberis vulgaris*, Metabolic disorders, Berberine, Anti-diabetic, Anti-hyperlipidemic

1. INTRODUCTION

A worldwide health problem is being exacerbated by the interconnectedness of metabolic illnesses, which encompass diabetes, hypertension, and hyperlipidaemia. Healthcare systems around the globe are facing tremendous challenges due to the increasing occurrence of these ailments, which are caused by inactive lifestyles, poor food choices, and genetic predispositions [1]. Insulin resistance, oxidative stress, as well as chronic inflammation are frequently interrelated pathologies. There is an immediate need for safer, multi-targeted therapeutic solutions because pharmaceutical treatments are available, but they are frequently ineffective due to high prices, side effects, and a failure to address the underlying reasons [2]. Nature has long served as a source of remedies for complex health conditions. Among such natural resources, *Berberis vulgaris* (commonly known as barberry) has stood out due to its rich pharmacological profile and historical use in traditional medicine systems. The plant is abundant in berberine, a bioactive alkaloid known for its diverse therapeutic effects [3]. *B. vulgaris* has demonstrated anti-diabetic properties by modulating glucose metabolism, anti-hypertensive effects through vascular relaxation, and anti-hyperlipidemic activity by reducing cholesterol and triglycerides. Furthermore, its antioxidant, anti-inflammatory, and microbiome-modulating capabilities make it a holistic candidate for addressing the multifactorial nature of metabolic disorders [4].

The purpose of this review is to give a comprehensive analysis of *B. vulgaris* and its possible function in the treatment and prevention of metabolic diseases. The purpose of this review is to provide *B. vulgaris* as a potential alternative to traditional treatments by exploring its phytochemical richness, molecular mechanisms, and clinical evidence. This will help to establish its place in contemporary healthcare methods [5].

2. Phytochemistry and Bioactive Compounds

2.1 Key Bioactive Compounds

Berberis vulgaris possesses multiple pharmaceutical characteristics attributed to its various bioactive substances particularly alkaloids and tannins and flavonoids and phenolic acids (Fig. 1). The therapeutic alkaloid berberine stands out as the leading scientist-researched molecule due to its ability to combat inflammation and diabetes while controlling raised lipid levels of Fat within the body [6]. The plant's therapeutic worth

increases through the regulatory action of berbamine which controls cholesterol levels and blood pressure. *B. vulgaris* possesses anti-inflammatory and antioxidant flavonoids along with its alkaloids. The compound tannins help people manage blood lipids and make insulin work better [7]. The vascular benefits of the plant stem from its ability to support endothelial function and destruct free radicals while protecting blood vessels through its phenolic acid content. These substances when combined present a system-wide approach to manage metabolic medical conditions [8].

2.2 Mechanisms of Action

Therapeutic effects of *B. vulgaris* stem from its ability to modify multiple cellular pathways. The anti-inflammatory plant properties *of B. vulgaris* stem from berberine and flavonoids which inhibit systemic inflammation through their reduction of cytokines TNF-α and IL-6 and other pro-inflammatory markers [9]. Metabolic tissues benefit from antioxidant activity of phenolic chemicals because these compounds function to neutralize harmful free radicals. By modulating two key enzymes the natural compound berberine indirectly reduces blood glucose and cholesterol levels. The plant utilizes multiple mechanisms for improved therapeutic outcomes with metabolic diseases [10].

2.3 Therapeutic Relevance

The therapeutic benefits of *B. vulgaris* against essential metabolic syndrome elements like hyperglycemia hypertension and dyslipidaemia demonstrate how plant phytochemicals contribute to therapeutic effects (Table 1). Multiple chemical compounds such as berryerin together with flavonoids and tannins and phenolic acids function collaboratively to enhance glucose metabolism and regulate blood pressure and manage lipid profiles [11]. *B. vulgaris* produces a holistic therapeutic framework to tackle metabolic disorders simultaneously beside its distinct therapeutic benefits. Its dual-action mechanism attacking multiple disease-causing pathways positions B. vulgaris as an appealing natural therapy which might serve as a suitable alternative to conventional medical interventions [12].

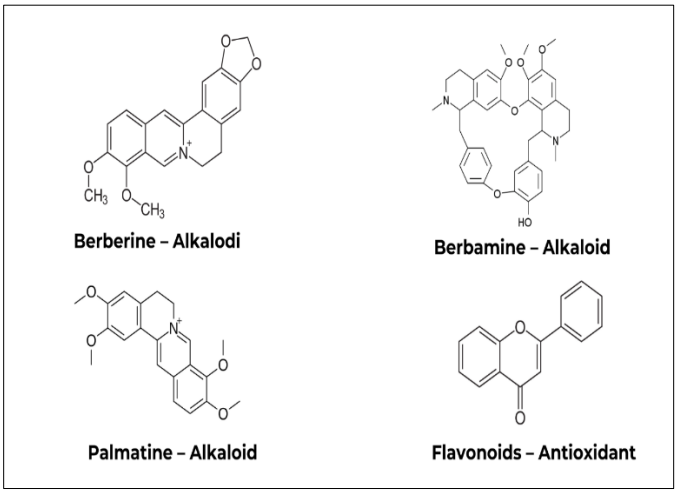

Figure 1: Key bioactive compounds and their chemical structures. [13]

Table 1: Comprehensive list of phytochemicals in *Berberis vulgaris* (compound, class, activity). [14]

Compound	*Class*	*Activity*
Berberine	Alkaloid	Anti-diabetic, anti-inflammatory, anti-hyperlipidemic, antioxidant
Berbamine	Alkaloid	Anti-hypertensive, anti-inflammatory
Quercetin	Flavonoid	Antioxidant, anti-inflammatory, anti-hypertensive
Kaempferol	Flavonoid	Antioxidant, anti-inflammatory, anti-cancer
Ellagic acid	Phenolic acid	Antioxidant, anti-inflammatory, cardiovascular protection
Ferulic acid	Phenolic acid	Antioxidant, anti-inflammatory, vasoprotective
Caffeic acid	Phenolic acid	Antioxidant, anti-inflammatory, anti-cancer
Tannins	Polyphenolic	Antioxidant, anti-inflammatory, lipid-lowering
Proanthocyanidins	Flavonoid	Antioxidant, anti-inflammatory, vascular health
Isoquinoline	Alkaloid	Anti-inflammatory, antibacterial
Columbamine	Alkaloid	Anti-inflammatory, anti-hypertensive
Hydroxycinnamic acid	Phenolic acid	Antioxidant, anti-inflammatory, liver protection

3. Anti-Diabetic Effects of *Berberis vulgaris*

3.1 Mechanisms of Action

Active ingredient berberine remains the key active pharmacological agent responsible for the anti-diabetic properties of *Berberis vulgaris.* A vital cellular process brings about activation of AMP-activated protein kinase (AMPK) to regulate energy balances inside cells. AMP-activated protein kinase (AMPK) activation enhances insulin sensitivity by reducing hepatic glucose production while simultaneously increasing peripheral glucose absorption rates [15]. Research shows that *B. vulgaris* step-ups its blood glucose level reduction potency through protein regulation of key glucose metabolic enzymes including phosphoenolpyruvate carboxykinase (PEPCK). *B. vulgaris* offers dual action to people with type 2 diabetes by functioning as an AMPK inhibitor while providing antioxidant and anti-inflammatory protection against oxidative stress and low-grade inflammation [16]. The support of insulin action and glucose homeostasis occurs indirectly through *B. vulgaris* which reduces adverse conditions. The collective molecular pathways suggest *B. vulgaris* demonstrates potential as a natural intervention for managing type 2 diabetes (Fig. 2) [17].

3.2 Preclinical Studies

The effectiveness of *Berberis vulgaris* as a blood glucose regulator for metabolic dysfunction treatment stands established after multiple preclinical research validating its glycaemic properties [18]. *In vitro* studies demonstrate that berberine harbours the dominant bioactive alkaloid existence in *B. vulgaris* which reduces intestinal carbohydrate digestion and absorption processes thus producing lowered blood glucose levels after eating by blocking enzymes such as α-glucosidase and α-amylase. Research evidence supporting the plant's medicinal value comes from experiments conducted with diabetic animal subjects [19]. Animal tests demonstrate that

diabetic rats show improvements in insulin sensitivity and measures of insulin resistance characterized by decreased HOMA-IR scores together with enhanced blood glucose reduction following treatment with *B. vulgaris*. People who receive *B. vulgaris* supplementation notice better insulin levels because it can restore pancreatic β-cell functions that are weakened. The improved lipid profile which includes reduced total cholesterol and triglycerides stands as an appealing treatment alternative for those with metabolic syndrome conditions. Evidence presented so far suggests that *B. vulgaris* warrants serious evaluation as an effective and natural diabetic treatment supplement [20].

3.3 Clinical Trials

The *B. vulgaris* extract proves beneficial for treating type 2 diabetes based on broad-based clinical trial findings. Different human trials administering *B. vulgaris* extracts containing berberine at various daily dosages between 500 and 1500 mg have occurred. Results from clinical trials demonstrate that fasting blood glucose (FBG) and haemoglobin A1c (HbA1c) normally show marked improvement during these trials [21]. Research shows *B. vulgaris* produces equivalent HbA1c results as first-line oral hypoglycemic drugs such as metformin while reducing this measure by 1.5% over 12 weeks. *B. vulgaris* holds promise as a metabolic health agent because it helps regulate lipid processes to reduce participants' levels of total cholesterol combined with LDL cholesterol and triglycerides [22]. Research indicates *B. vulgaris* benefits patients through enhanced liver performance besides reducing their stress-mediated biomarkers. Worldwide understanding of *B. vulgaris* therapy for diabetes demands further extensive scientific inquiry of safety measures along with additional long-term testing yet available experimental findings remain positive. Topper might offer several advantages as a new tool for type 2 diabetes management even though its primary benefit currently appears to be blood sugar reduction [23].

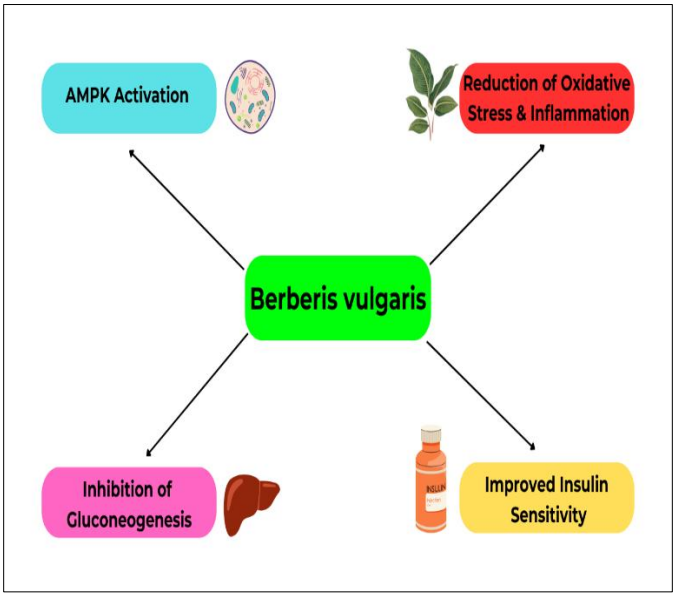

Figure 2: Schematic representation of anti-diabetic pathways modulated by *Berberis vulgaris*. [24]

4. Anti-Hypertensive Effects of *Berberis vulgaris*

4.1 Mechanisms of Action

Berberine together with other active compounds in *Berberis vulgaris* act as blood pressure regulators through their activation of various pathways controlling hypertension. Increasing NO production initiates two important biological cascades that lead to vasodilation and decreased vascular resistance which ultimately promotes a decrease in blood pressure [25]. *B. vulgaris* demonstrates multiple worthwhile benefits through its dual action as a blood pressure reducer and against inflammation. Studies show that continuous low-grade inflammation stands as a primary factor in raising hypertension levels. Through its anti-inflammatory mechanisms *B. vulgaris* shows promise as a treatment for hypertension-triggering endothelial dysfunction [26]. The renin-angiotensin-aldosterone system that controls blood pressure regulation shows changes when an individual consumes *B. vulgaris*. Levels of the powerful vasoconstrictor angiotensin II decrease when berberine inhibits the RAAS resulting in lowered blood pressure and vasodilatory effects. *B. vulgaris* demonstrates potential to serve as a natural management tool for hypertension through its identified biochemical processes [27].

4.2 Preclinical Evidence

Preclinical studies of *Berberis vulgaris* as an anti-hypertensive agent find confirmation through experiments on hypertension models with laboratory animals. Research on hypertensive rats proved that berberine administration achieves significant blood pressure reduction in every vascular measurement point [28]. Three main factors drive blood pressure declines through increased nitric oxide availability along with enhanced endothelial function combined with reduced vascular resistance. Research evidence supporting vasodilative effects of *B. vulgaris* shows laboratory observations indicating this plant can relax isolated blood vessels [29]. The study of *B. vulgaris* demonstrates its potential to reduce blood pressure after showing positive effects on heart rate variability measurements which indicate autonomic nervous system function. Preclinical studies indicate *B. vulgaris* might become an effective natural option for managing hypertension however additional clinical research is needed [30].

4.3 Potential Clinical Applications

The human clinical data about Berberis vulgaris as a hypertension medicine remains scarce but multiple preclinical experiments demonstrate its potential as an antihypertensive agent. The evidence suggests *B. vulgaris* might be beneficial for managing hypertension as an additional treatment method [31]. The human trials show promising results about berberine supplementation which leads to diminished readings of systolic and diastolic blood pressure. Larger well-designed clinical trials of *B. vulgaris* in hypertension patients must proceed to verify these findings and establish the proper dosage levels and extended safety and potency characteristics of this herb [32]. Future trials should study the effects of *B. vulgaris* on endothelial function while evaluating arterial stiffness together

with assessment of potential interactions with other anti-hypertensive drugs. Evidence about *B. vulgaris's* effects is scarce yet studies imply it could serve as both an alternative medicine and an additional treatment option for traditional hypertensive drugs [33,34].

5. Anti-Hyperlipidemic Effects of *Berberis vulgaris*

5.1 Mechanisms of Action

The plant *Berberis vulgaris* can help regulate lipid metabolism and thus improve dyslipidaemia along with its main ingredient berberine. Berkeleyrine acts to inhibit cholesterol synthetic pathway through blocking the rate-limiting process of HMG-CoA reductase which stands as a primary mechanism of its anti-hyperlipidemic action [35]. Total cholesterol decreases as the final outcome of this process. LDL-C removal becomes more efficient through berberine administration which activates LDL receptor expression. The consumption of berberine leads to reduced total cholesterol levels through improved fatty acid digestion mechanisms that also stabilize lipid synthetic processes. Thanks to *B. vulgaris* a person can lower their total cholesterol and LDL-C and triglyceride levels and many cases experience an increase in HDL-C levels [36].

5.2 Preclinical Studies

Multiple animal models indicate that *Berberis vulgaris* substantially affects the regulation of body lipids. The research on hyperlipidemic rats and mice reveals that berberine supplement intake effectively decreases total cholesterol and LDL-C and triglycerides but increases the HDL-C level. When given to rats with induced hyperlipidaemia berberine reduced cholesterol by forty percent while decreasing triglycerides by thirty-five percent [37]. The rise in HDL-C and reduction of LDL-C occur due to enhanced cholesterol elimination from the body through the process of reverse cholesterol transport. Research shows that berberine regulates lipid metabolism as well as producing extensive influences on glucose and fat oxidation through the activation of AMP-activated protein kinase (AMPK). Preliminary findings suggest that *B. vulgaris* shows potential to become an effective natural treatment for patients with hyperlipidaemia as well as cardiovascular disease risks [38].

5.3 Clinical Trials

Scientific research using human participants demonstrated that *Berberis vulgaris* effectively lowers levels of cholesterol in biological systems. The administration of berberine as a supplement over four to six weeks decreased total cholesterol together with LDL-C and triglycerides among study participants with high cholesterol. The elevation of HDL-C levels implies that berberine showed equivalent effects on lipid metabolism in humans as it did in laboratory animals [39]. The combination therapy between berberine and statins produced additive effects on lipid profiles yet did not enable significant reduction of prescribed statins in specific trials. Additional big randomized controlled clinical trials need to confirm the entire therapeutic power of *Berberis vulgaris* to reduce lipids and manage hyperlipidaemia because current studies have shown promising results. Scientific teams should study *B. vulgaris* potential for both dyslipidaemia treatment and statins supplementation therapy [40].

6. Safety and Toxicity

6.1 Toxicity Profiles

Multi-dimensional toxicity evaluations have proven *Berberis vulgaris* together with berberine as safe substances for therapeutic use. Animal models exist for evaluating *Berberis vulgaris* safety through toxicity examinations that include acute, subacute and chronic toxicity tests. Laboratory tests reveal that berberine presents no lethal effects since doses as high as 2000 mg/kg did not lead to rat deaths [41]. The research on berberine acute toxicity demonstrates its security for temporary consumption because it does not cause alterations to haematological, biochemical, or histopathological markers. The long-term effects of berberine consumption revealed that extremely high dosage levels exceeding 1000 mg/kg/day could lead to moderate gastrointestinal issues which cause diarrhea but these symptoms are generally mild. The prolonged therapeutic application of berberine shows no evidence of organ damage making it acceptable for extended usages at moderate dosage. [42].

6.2 Safe Dosage Ranges

The recommended therapeutic dose of berberine obtained from *Berberis vulgaris* exists between 500 mg to 1500 mg daily per day according to preclinical and clinical research that confirmed its safety. Clinical trials indicate that blood glucose levels and lipid profiles and blood pressure will improve within therapeutic berberine doses found safe in these trials [43]. The recommended treatment amount for diabetes and hyperlipidaemia patients consists of 500 mg to 1000 mg taken two or three times each day. Safe and well-tolerated quantities of these drugs exist in human medicine but therapy type affects what amounts will be appropriate. Medical professionals should customize berberine dosage for individual patients by considering their medical background combined with treatment outcomes alongside body weight [44].

6.3 Potential Adverse Effects

Berberis vulgaris along with berberine provides beneficial medical outcomes but introduces possible harmful effects which proportionally increase with dosage elevation. Gastrointestinal side effects from *Berberis vulgaris* therapy primarily result in mild to moderate symptoms of diarrhea, constipation, stomach pain and bloating. The side effects tend to disappear when patients decrease medication levels or end treatment [45]. Some liver enzymes handle drug metabolism through cytochrome P450 but berberine might have an interaction with these metabolizing enzymes. Some examples of drugs including Cyclosporine and statins and anticoagulants demonstrate potential drug interactions which might lead to unfavorable side effects. The glucose-lowering effects of berberine create a higher chance of developing hypoglycemia

because it strengthens the actions of other diabetes medication. [46]. Patients using berberine in conjunction with anti-diabetic medications should have their blood glucose levels monitored frequently. Because of the lack of evidence about berberine's safety during pregnancy, it is widely recommended that pregnant and breastfeeding women avoid using it. So, although berberine is usually safe for most people, there are some groups that should be cautious when using it because of possible drug interactions [47].

7. Challenges and Future Directions

7.1 Gaps in Current Research

Research demonstrates that *Berberis vulgaris* shows potential benefits for metabolic disease prevention along with treatment but additional inquiries remain unanswered throughout the current literature. Developing planned human clinical studies presents the major obstacle in modern research. The current research yields result which cannot be generalized across groups because most studies have small sample sizes and brief durations as well as insufficient geographic distribution [48]. Additional research needs to establish *B. vulgaris* safety parameters for the prevention and treatment of long-term diabetes and hypertension and hyperlipidaemia conditions through standardized controlled studies [49].

Multiple factors impair the comparability of *B. vulgaris* formulations since different trials utilize different *B. vulgaris* preparations. Analysing research data becomes challenging because there is no standardization regarding *Berberis vulgaris* extraction methods alongside dosage amounts and delivery methods [50]. Additional investigations regarding *B. vulgaris* extract's consistency between potency and bioavailability must occur before establishing standard manufacturing techniques can be established. Researchers need to undertake further investigations to both identify whole bioactive compounds and separate individual effective components from *B. vulgaris* with a focus on berberine since this will help develop specific therapeutic treatments [51].

7.2 Future Research Opportunities

Research on *Berberis vulgaris* needs additional investigation of treatment enhancement through cooperation with conventional medicine. Patients may experience enhanced medical results as well as decreased synthetic drug impacts through combining *B. vulgaris* with standard therapeutic options that manage metabolic diseases. Using customised patient genetics in medicine practice allows *B. vulgaris* to provide optimal therapy for metabolic disorders [52].

The study of *B. vulgaris's* impact on different biological pathways would be improved through comprehensive investigation of metabolic mechanisms at a molecular level by using genomics, proteomics, and metabolomics technologies [53]. Medical researchers can use this discovery to develop personalized medicines effective with less adverse effects. The medical effectiveness of *B. vulgaris* chemicals would improve through novel nano-formulations such as nanoparticles or Nano emulsions that increase drug absorption in the body with sustained-release properties [54].

CONCLUSION

The herbal medicine known as *Berberis vulgaris* has significant promise to treat metabolic diseases that include diabetes and both hypertension and high cholesterol levels. Through its bioactive compounds especially berberine the main metabolic functions including glucose management alongside lipid regulation and blood pressure alignment receive targeted biological activation. *Berseris vulgars* demonstrates usefulness as an adjunct treatment against metabolic diseases because its insulin sensitizing properties combined with blood pressure management and lipid profile improvement effects stem from AMPK activation and nitric oxide regulation and HMG-CoA reductase enzyme inhibition.

Despite the encouraging results, there are still significant gaps in the current literature, especially when it comes to standardised *B. vulgaris* formulations and large-scale human studies. To confirm its safety and effectiveness across various demographics and to develop final treatment recommendations, more extensive clinical trials are required. Furthermore, new drug delivery technologies and the investigation of synergistic combinations with existing treatments have the potential to greatly improve its therapeutic efficacy and clinical utility.

In conclusion, *Berberis vulgaris* holds substantial therapeutic potential in the management of metabolic disorders, and future research should focus on addressing the current gaps to unlock its full capabilities. Its integration into modern therapeutic strategies, alongside conventional treatments, could offer an effective, natural alternative for improving metabolic health and combating the global burden of metabolic diseases.

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