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BERBERINE: A PROMISING PHYTOCHEMICAL WITH MULTIFUNCTIONAL PHARMACOLOGICAL ACTIVITIES AND FUTURE THERAPEUTIC POTENTIAL

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ABSTRACT

Berberine is a natural isoquinoline alkaloid primarily isolated from various medicinal plants such as *Berberis vulgaris*, *Coptis chinensis*, and *Hydrastis canadensis*. It has been extensively used in traditional Chinese and Ayurvedic medicine for centuries due to its diverse therapeutic potential. Phytochemically, berberine possesses a quaternary ammonium salt structure belonging to the protoberberine group of alkaloids, responsible for its strong yellow coloration and bioactivity. Modern pharmacological studies have demonstrated that berberine exhibits wide-spectrum biological activities including antimicrobial, antidiabetic, anti-inflammatory, antioxidant, anticancer, hypolipidemic, hepatoprotective, neuroprotective, and cardioprotective effects. Its molecular mechanisms involve modulation of multiple signalling pathways such as AMPK activation, NF-KB inhibition, and regulation of oxidative stress and apoptosis. Despite its promising pharmacological profile, berberine's poor aqueous solubility, low bioavailability, and rapid metabolism limit its clinical translation. Recent nanotechnological approaches such as nanoemulsions, liposomes, nanoparticles, and solid lipid systems have been developed to enhance its bioavailability and therapeutic efficacy. Future research should focus on optimizing delivery systems, exploring synergistic herbal combinations, understanding pharmacogenomic responses, and conducting more extensive clinical trials to establish safety and efficacy. Berberine thus represents a potent phytochemical with multifaceted pharmacological activities and immense potential for future drug development and clinical applications

KEYWORDS: Berberine; Isoquinoline alkaloid; Phytochemical; Antimicrobial; Antidiabetic; Antioxidant; Anti-inflammatory; Bioavailability.

1. INTRODUCTION

Berberine is a naturally occurring compound from the roots and stem bark of protoberberine family is isoquinoline alkaloids. It is extracted from various medicinal plants such as *Hydrastis canadensis*, *Tinospora cordifolia*, *Berberis aristata*, and *Berberis vulgaris*. Berberine is known for its bright yellow color, berberine has been used for centuries in traditional medicine to treat wounds, inflammation, metabolic issues, liver problems, digestive disorders, and infections. Over the past 20 years, it has regained attention as a compound of significant pharmacological value due to its ability to interact with multiple molecular targets and signalling pathways.

Recent studies have shown that berberine has strong biological effects, including lowering blood sugar, reducing cholesterol and triglycerides, fighting oxidative stress, reducing inflammation, killing harmful microbes, protecting the nervous system, and fighting cancer. Because of its ability to target multiple areas of the body, it is considered a promising treatment for complex diseases like metabolic syndrome, type 2 diabetes, atherosclerosis, neurodegenerative disorders, and various cancers.

One of the best-known ways berberine works is by activating AMPK, a key molecule that controls cellular energy balance. When AMPK is activated, it increases mitochondrial activity, fatty acid breakdown, and

glucose uptake while reducing fat production and glucose formation.[1] Many studies from 2018 to 2025 have shown that berberine lowers fasting blood sugar, HbA1c, LDL cholesterol, and triglycerides in people.[2] It also reduces inflammation by blocking the NF-κB and MAPK pathways, which lowers oxidative stress and reduces harmful cytokine production.[3,4]

Berberine also changes the gut microbiome by promoting the growth of good bacteria and reducing harmful ones.This is important because gut health is closely connected to liver function and plays a key role in improving metabolic conditions.[5] In cancer research, berberine has been shown to stop blood vessel growth, prevent cells from dividing, cause cell death, and block the spread of cancer cells in different models.[6,7]

Despite its strong pharmacological effects, berberine has limited use in clinical settings because of its very low oral absorption, less than 1%. This is due to factors like poor solubility, a rigid molecule structure, P-glycoprotein pumps that expel it, and quick metabolism in the liver and gut. To make it more effective, scientists have developed advanced drug delivery systems, including nanoemulsions, phytosomes, liposomes, and polymeric nanoparticles, which have improved its bioavailability and drug-like properties.[8,9]

Because of its broad range of effects, multiple organ benefits, and growing evidence, berberine remains an attractive candidate for future drug development. This review thoroughly examines its chemical properties, pharmacological effects, challenges, and new therapeutic uses.[10]

2. PHYTOCHEMICAL DETAILS

Berberine is a type of alkaloid called a protoberberine, which is part of the isoquinoline group. It mostly exists as a quaternary ammonium salt, which gives it a bright yellow, crystalline look. Its ability to affect the body comes from a flat, four-ring structure in its molecule, with specific groups like methoxy and methylenedioxy attached. The IUPAC name for this structure is 9,10-dimethoxybenzo[g]5,6-dihydro-1,3-benzodioxolo[5,6-a]quinolizium.

2.1 Structure of Berberine

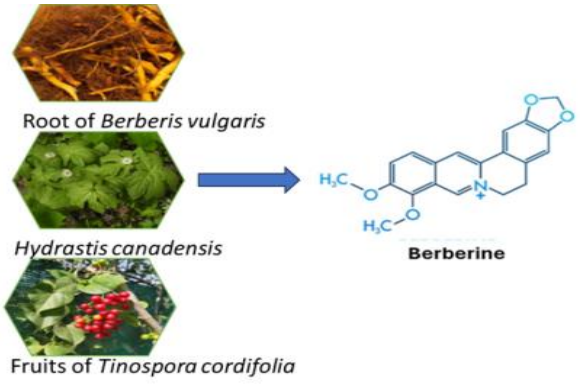

Figure 1: Schematic representation of Berberine.

The chemical formula of berberine is C22H24NO4+ with a molecular weight of 336.36 grams per mole.

The melting point ranges from 145-146°C. It is very less soluble in water but have good good in alcohol, methanol, and DMSO. It has a bitter taste and shows strong fluorescence when exposed to UV light. It is very stable in its crystalline form.

2.2. Primary Natural Sources

The primary source of berberine are *Berberis vulgaris*, *Tinospora cordifolia*, *Coptis chinesis*, *Hydrastis canadensis*, *Berberis aristate*. The physicochemical parameters are listed in table 1.

Table 1: Physical parameters of berberine.

Parameter	Description
Class	Protoberberine alkaloid
Color	Bright yellow
Molecular Weight	336.36 g/mol
Solubility	Poor in water, moderate in alcohol
Functional groups	Methoxy, methylenedioxy
Fluoresence	Strong under UV
Stability	Highly stable alkaloid

3. MULTIFUNCTIONAL PHARMACOLOGICAL PROPERTIES

3.1 Antidiabetic and Metabolic Effects

Berberine is one of the most studied phytochemicals for treating metabolic diseases and diabetes. Its main way of helping with diabetes is by activating AMP-activated protein kinase, or AMPK, which plays a big role in how cells manage energy. When AMPK is activated, it helps the body become more sensitive to insulin and balance metabolism by boosting the breakdown of fatty acids, supporting mitochondrial function, reducing glucose production in the liver, and increasing glucose uptake in muscles.[11,12] Berberine has been shown to be just as effective as metformin in treating type 2 diabetes. It helps lower fasting blood sugar, blood sugar after meals, HbA1c levels, triglycerides, and LDL cholesterol, as found in many clinical studies.[12,13] One of the key benefits of berberine is its ability to increase the movement of GLUT4, a protein that helps cells absorb glucose, in muscle and fat tissues.This leads to less insulin resistance and better use of glucose in the body.[14] It also improves mitochondrial function and cuts down on oxidative stress in tissues that respond to insulin, which helps people with diabetes and obesity manage their metabolism better.[15] Berberine also plays a big role in managing lipid metabolism. By affecting pathways like AMPK, mTOR, and SREBP-1c, it stops fat cells from forming, reduces fat production, increases fat breakdown, and lowers fat buildup in the liver.[16] These actions help reduce dyslipidemia, a common problem in diabetes. Another important way berberine works is by changing the gut microbiome. It reduces harmful bacteria and increases good ones, such as Bifidobacterium and Akkermansia muciniphila. This change encourages the production of short-chain fatty

acids, lowers harmful substances in the blood, improves gut health, and reduces inflammation that is linked to insulin resistance.[17,18] Taking berberine by mouth is a promising option as a complement or alternative to standard diabetes treatments. It effectively lowers fasting blood sugar and HbA1c, improves insulin sensitivity, and supports better lipid metabolism without causing major side effects, as shown in meta-analyses and clinical trials Berberine has many benefits for metabolism, which shows it could be very useful in treating conditions like metabolic syndrome, type 2 diabetes, obesity, and non-alcoholic fatty liver disease (NAFLD).[19,20]

3.2 Cardioprotective Effects

Berberine is a promising treatment for various cardiovascular conditions such as atherosclerosis, dyslipidemia, hypertension, heart failure, and arrhythmias. This is due to its strong ability to[18] zprot[14] zect the heart through several related mechanisms. One key way it works is by improving lipid metabolism. Berberine helps by keeping the LDL receptor (LDLR) mRNA stable and increasing the expression of LDLR in liver cells.[21] This leads to lower levels of total cholesterol, LDL-C, and triglycerides, helping the body remove more cholesterol from the blood.[22] Clinical studies show that berberine can reduce serum lipid levels similarly to traditional statins, but with fewer side effect. Another important effect is its ability to prevent oxidative stress, endothelial dysfunction, and vascular inflammation, which are linked to atherosclerosis.[23] Berberine boosts the production of nitric oxide (NO), which is crucial for blood vessel relaxation and proper blood flow, by increasing the activity of endothelial nitric oxide synthase (eNOS). Additionally, berberine stops the activation of NF-κB and MAPK pathways, reduces the formation of foam cells, and lowers reactive oxygen species (ROS), all of which help prevent vascular inflammation and plaque growth.[24] Berberine also offers protection through its anti-inflammatory and antioxidant properties. It lowers levels of inflammatory markers such as TNF-α, IL-6, CRP, and adhesion molecules, which improves vascular function and reduces the risk of endothelial damage. In stressful situations like ischemia-reperfusion injury, berberine helps heart muscle cells survive by regulating mitochondrial function and preventing oxidative damage to mitochondria.[25] Berberine also has anti-arrhythmic properties. Research shows it helps maintain a steady heart rhythm by controlling calcium levels in heart muscle cells and blocking certain potassium currents (IKr), which stabilizes the heart's electrical activity and reduces the risk of dangerous ventricular arrhythmias.[26] In heart failure models, berberine improves cardiac function by modifying pathways like TGF-β and PI3K/Akt, which reduce heart muscle thickening, lower cardiac remodeling, and enhance the heart’s ability to contract Improved endothelial function and reduced oxidative stress further support better heart performance. Berberine's wide range of benefits, including lowering lipids, reducing inflammation, fighting oxidative stress, preventing atherosclerosis, controlling arrhythmias.[27,28]

3.3 Antimicrobial activity

Berberine has strong antimicrobial effects against many types of harmful microorganisms, including bacteria, fungi, protozoa, and certain viruses. It works by damaging the cell membranes of these microbes, stopping them from making DNA and proteins, and interfering with important processes they need to survive.[29] One of the ways it kills bacteria is by attaching to their DNA, stopping them from dividing and preventing enzymes called topoisomerases from working properly. Berberine is effective against a wide range of bacteria, both Gram-positive and Gram-negative, such as Helicobacter pylori, Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus.[30] One of its key advantages is that it can block certain proteins, like NorA and MdfA, which help bacteria become resistant to antibiotics. When used together with antibiotics such as ciprofloxacin, tetracycline, and azithromycin, berberine can make these drugs more effective by stopping the bacteria from expelling them.[31] This makes berberine a promising option in the fight against drug-resistant bacteria, which is a major health challenge today. Berberine also fights fungi by weakening their cell walls, disrupting the production of a substance called ergosterol that is important for their structure, and stopping the growth of fungal threads.[32] It has shown effectiveness against fungi like dermatophytes, Aspergillus niger, and Candida albicans. In addition, it can harm the energy-making processes in parasites and stop their DNA from replicating, making it useful against protozoa like Leishmania and Plasmodium species.[33] Overall, berberine shows great promise as a natural antimicrobial agent and could be an effective alternative for treating drug-resistant infections. Its ability to disrupt microbial membranes, block resistance mechanisms, and interfere with metabolic processes makes it a versatile and powerful tool in the fight against various infectious diseases.[34]

3.4 Anti-cancer activity

Berberine shows strong anticancer effects in various types of cancer, including breast, lung, colon, liver, prostate, and ovarian cancers. It works by changing several key signaling pathways that are involved in the start, growth, and spread of tumors. One of the main ways it fights cancer is by activating the intrinsic mitochondrial pathway, which leads to programmed cell death, or apoptosis. In cancer cells, berberine causes this by increasing the ratio of Bax to Bcl-2, promoting the release of cytochrome c, and activating caspase-3 and caspase-9.[35] Additionally, berberine stops cancer cells from growing uncontrollably by reducing the activity of cyclins and cyclin-dependent kinases (CDKs), which causes cell cycle arrest at either the G1 or G2/M phase.[36] It also lowers cancer cell survival, limits the formation of new blood vessels that feed tumors, and helps cancer cells become more sensitive to

chemotherapy by blocking key pathways like PI3K/Akt, MAPK/ERK, Wnt/β-catenin, and mTOR.[37,38] Berberine also has anti-metastatic effects, as it prevents cancer cells from moving and invading surrounding tissues, reduces the levels of matrix metalloproteinases (MMP-2 and MMP-9), and stops the process of epithelial-to-mesenchymal transition (EMT).[39] Moreover, it has strong anti-angiogenic properties, as it reduces the production of VEGF and HIF-1α, which are important for the growth of blood vessels that support tumor growth.[40]

3.5 Neuroprotective Effects

Berberine exhibits significant neuroprotective potential and has been extensively studied for neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), stroke, depression, and cognitive impairment. Its neuroprotective actions are mediated through multiple mechanisms, including antioxidant, anti-inflammatory, anti-amyloid, and mitochondrial-stabilizing effects. In Alzheimer's disease, berberine reduces amyloid-beta (Aβ) accumulation by inhibiting β-secretase (BACE1) and enhancing Aβ clearance pathways. It also prevents tau protein hyperphosphorylation through modulation of GSK-3β signaling, thereby protecting synaptic integrity and cognitive function.[41,42] In Parkinson's disease models, berberine protects dopaminergic neurons by reducing oxidative stress, inhibiting α-synuclein aggregation, and improving mitochondrial function. It enhances dopamine levels and improves motor coordination by regulating PI3K/Akt and Nrf2 pathways, promoting neuronal survival under oxidative damage.[43] Berberine also demonstrates strong neuroprotective activity in ischemic stroke. It reduces neuronal apoptosis, suppresses excitotoxicity, and restores mitochondrial membrane potential, resulting in decreased infarct size and improved functional outcomes. Its anti-inflammatory effects, particularly inhibition of NF-κB and reduction of cytokines such as IL-6 and TNF-α, further contribute to neuronal protection during ischemic injury.[44] Additionally, berberine shows antidepressant-like effects by modulating monoamine neurotransmitters and enhancing synaptic plasticity through upregulation of BDNF expression.[45] Overall, berberine's multi-targeted mechanisms—including antioxidant defense, anti-inflammatory modulation, amyloid inhibition, and mitochondrial stabilization—highlight its strong therapeutic potential in neurodegenerative and neurological disorders.

3.6 Anti-inflammatory ad Antioxidant Effects

Berberine exhibits potent anti-inflammatory and antioxidant activities, which play a central role in its therapeutic potential for chronic metabolic, cardiovascular, and neurodegenerative diseases. One of the primary anti-inflammatory mechanisms involves inhibition of the nuclear factor-kappa B (NF-κB) signaling pathway, a master regulator of pro-inflammatory cytokines. Berberine suppresses the expression of TNF-α, IL-6, IL-1β, COX-2, and iNOS, thereby reducing systemic and tissue-specific inflammation.[46] It also interferes with MAPK signaling by downregulating ERK, JNK, and p38 pathways, resulting in decreased inflammatory mediator production.[47] Berberine exerts strong antioxidant effects by enhancing the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx).[48] It activates the Nrf2-Keap1 pathway, promoting the transcription of phase II antioxidant enzymes and reducing oxidative stress in cells exposed to free radicals or metabolic injury.[49] This antioxidant defense mechanism helps protect tissues from lipid peroxidation, protein oxidation, and DNA damage. In metabolic and cardiovascular disorders, berberine reduces oxidative stress markers such as malondialdehyde (MDA) and reactive oxygen species (ROS), thereby improving endothelial function and preventing vascular inflammation.[50] In neurodegenerative models, berberine attenuates oxidative neuronal injury, reduces mitochondrial ROS production, and enhances neuronal resilience.[51] Together, berberine's dual anti-inflammatory and antioxidant properties contribute significantly to its broad therapeutic effects and make it a promising natural compound for diseases driven by chronic inflammation and oxidative imbalance.

Table 2: Summary of pharmacological action.

Activity	Mechanism	References
Antidiabetic	AMPK activation	(52)
Cardioprotective	Antiarrhythmic, lipid reducing	(53)
Antimicrobial	Efflux pump inhibition	(54)
Anticancer	Apoptosis, P13K inhibition	(55)
Neuroprotective	Anti-amyloid, antioxidant	(56)
Anti-inflammatory	NF-KB inhibition	(57)

4. CHALLENGES AND LIMITATION OF BERBERINE

Despite its broad therapeutic potential, berberine's clinical translation is restricted by several pharmacokinetic and practical limitations. The most significant challenge is its extremely low oral bioavailability, reported to be less than 1%, largely due to poor aqueous solubility, limited intestinal permeability, and rapid first-pass metabolism in the liver and gut. Furthermore, berberine is extensively extruded by P-glycoprotein (P-gp) transporters in the intestinal epithelium, preventing efficient absorption and reducing its systemic exposure.[58,59] These factors collectively necessitate higher oral doses, which may contribute to an increased risk of adverse reactions.

Gastrointestinal intolerance is another major concern. Many patients experience diarrhea, abdominal cramps, nausea, and constipation, particularly when treated with

high doses or prolonged regimens. Such effects are attributed to berberine's impact on gut motility and microbial composition, often limiting patient adherence in chronic therapies such as diabetes and cardiovascular diseases.[60] Additionally, berberine is known to interact with cytochrome P450 enzymes and P-gp, raising the potential for herb–drug interactions with medications like antidiabetics, anticoagulants, and antihypertensives.[61] Another limitation involves the lack of standardized formulations. Commercial berberine products vary widely in purity and potency, making dose optimization challenging. Moreover, although preclinical data support its pharmacological actions, large, well-designed clinical trials are still limited, creating uncertainty regarding long-term safety and efficacy.[62] These limitations highlight the need for improved delivery systems—such as nanoparticles, phytosomes, and liposomes—to enhance berberine's solubility, absorption, and therapeutic outcomes.

6. FUTURE THERAPEUTIC POTENTIAL

Berberine possesses substantial future therapeutic potential due to its multi-target pharmacological actions and applicability across diverse disease conditions. One of the most promising areas is metabolic and cardiovascular health, where berberine has shown effects comparable to standard drugs such as metformin and statins. With advancements in nanotechnology—nanoemulsions, solid lipid nanoparticles, phytosomes, and liposomes—its low bioavailability barrier is being overcome, enabling enhanced absorption, controlled release, and improved therapeutic efficiency.[63,64] These novel formulations may establish berberine as a viable long-term therapy for diabetes, dyslipidemia, hypertension, and metabolic syndrome.

Berberine also demonstrates significant potential in oncology. Its ability to inhibit cancer cell proliferation, angiogenesis, and metastasis while inducing apoptosis provides a foundation for its use as an adjuvant to chemotherapy. Emerging research suggests synergistic effects when combined with drugs such as cisplatin, paclitaxel, and doxorubicin, indicating its value in reducing chemoresistance and enhancing treatment outcomes.[65]

In the field of neuroprotection, berberine's antioxidant and anti-inflammatory abilities, along with its effects on amyloid-beta reduction and mitochondrial stabilization, highlight its potential for managing Alzheimer's disease, Parkinson's disease, stroke, and cognitive decline. Nanocarriers capable of enhancing its brain penetration further expand its applicability in neurological therapy.[66]

Berberine is also emerging as a promising option for antimicrobial therapy, especially against multidrug-resistant pathogens. Its ability to inhibit bacterial efflux pumps and synergize with conventional antibiotics opens new avenues for future antimicrobial drug development.[66]

Overall, berberine's therapeutic potential is significantly enhanced by modern drug delivery advancements and expanding evidence from molecular and clinical research. Future large-scale trials and standardized formulations will be crucial in establishing berberine as a mainstream therapeutic agent in multiple disease domains.

CONCLUSION

Berberine is a multifunctional phytochemical with significant therapeutic promise across metabolic, cardiovascular, neurological, antimicrobial, and oncological domains. Its broad pharmacological effects are attributed to its ability to modulate key molecular pathways such as AMPK, NF-κB, PI3K/Akt, and Nrf2, alongside its influence on gut microbiota and mitochondrial stability. Despite these diverse benefits, berberine's clinical translation remains limited by poor oral bioavailability, rapid metabolism, and potential herb–drug interactions. However, recent advances in nanotechnology—including nanoemulsions, phytosomes, liposomes, and polymeric nanoparticles—have shown considerable potential in enhancing its solubility, permeability, and therapeutic activity. Continued development of standardized formulations and well-designed clinical trials will be critical to validating its long-term safety, optimal dosing, and efficacy. Overall, berberine represents a promising natural compound that, with improved delivery strategies and robust clinical evidence, may evolve into an important therapeutic agent for managing complex chronic diseases.

CONFLICTS OF INTEREST STATEMENT

Authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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