

Multi-target therapeutic potential of *Berberis vulgaris* in systems biology through harmonious healing

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Abstract

Berberis vulgaris, a medicinal plant rich in the isoquinoline alkaloid berberine, has emerged as a promising multi-target therapeutic agent with broad-spectrum pharmacological activities. This review integrates evidence from systems biology, network pharmacology, and experimental studies to elucidate the complex mechanisms underlying its therapeutic efficacy. Berberine operates as a network modulator, interacting with multiple molecular targets organized within protein–protein interaction (PPI) networks and influencing key signaling pathways such as AMPK, NF- κ B, PI3K–Akt, and MAPK. These interactions enable coordinated regulation of inflammation, metabolism, apoptosis, and cellular stress responses. A significant dimension of its activity involves modulation of the gut microbiota, where berberine reshapes microbial composition, enhances short-chain fatty acid production, regulates bile acid metabolism, and restores intestinal barrier integrity, collectively contributing to improvements in metabolic disorders including type 2 diabetes, obesity, and non-alcoholic fatty liver disease.

Additionally, berberine demonstrates potent synergistic effects with conventional antibiotics against multidrug-resistant (MDR) pathogens by inhibiting efflux pumps, disrupting biofilms, increasing membrane permeability, and re-sensitizing resistant strains. These properties position it as a valuable antibiotic adjuvant in addressing antimicrobial resistance. Besides, berberine exhibits significant neuroprotective effects in neurodegenerative disorders such as Alzheimer’s and Parkinson’s diseases. Its mechanisms include inhibition of amyloid-beta production, reduction of tau hyperphosphorylation, attenuation of oxidative stress and neuroinflammation, preservation of mitochondrial function, and modulation of neurotransmitter systems and the gut–brain axis. This integrative mode of action highlights its potential as a foundation for novel therapeutic strategies in metabolic diseases, infectious diseases, and neurodegenerative disorders.

Keywords: *Berberis Vulgaris*; Therapeutic Potential; Systems Biology; Metabolic Disorders

1. Introduction

A systems biology perspective of *Berberis vulgaris* emphasizes its role as a complex phytochemical system rather than a single-compound remedy. The plant contains a diverse array of isoquinoline alkaloids, including berberine, palmatine, berbamine, and berberrubine, each contributing to a broader pharmacological profile. Instead of acting on one molecular target, these compounds collectively interact with multiple proteins and genes, forming an intricate compound–target network (Kong et al., 2004; Tillhon et al., 2012). This network-based interaction reflects a key principle of systems biology: biological responses emerge from interconnected pathways rather than isolated events. High-throughput computational approaches such as network pharmacology and molecular docking studies have identified dozens of potential targets for berberine, including enzymes, receptors, and transcription factors involved in inflammation, metabolism, and cell survival (Zhou et al., 2020; Gu et al., 2019). Furthermore, omics-based analyses

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(transcriptomics and metabolomics) reveal that berberine induces global gene expression changes associated with energy homeostasis, oxidative stress response, and immune modulation (Wang et al., 2017). Such a framework helps explain why *Berberis vulgaris* exhibits wide-ranging therapeutic effects across metabolic, inflammatory, cardiovascular, and neurological disorders.

At the molecular level, the targets of *Berberis vulgaris* alkaloids are organized within protein-protein interaction (PPI) networks that highlight highly connected hub proteins. These hubs, serve as regulatory nodes controlling cellular processes like proliferation, apoptosis, and immune signaling (Hopkins, 2008; Li et al., 2021). When berberine and related compounds interact with these hubs, they influence entire cascades of downstream effects rather than single biochemical reactions. This multi-node modulation is particularly significant in chronic diseases, where dysregulation occurs across entire networks rather than isolated targets. Systems-level analyses have demonstrated that berberine can rewire signaling networks by modulating kinase activity and transcriptional regulators, thereby restoring disrupted cellular communication (Zhang et al., 2019). By stabilizing or rebalancing these networks, *Berberis vulgaris* functions as a system-level modulator capable of restoring physiological homeostasis.

Pathway enrichment analyses further reveal that the targets of *Berberis vulgaris* are concentrated in several critical biological pathways. These include inflammatory signaling pathways such as NF- κ B, JAK/STAT, and cytokine-cytokine receptor interactions; metabolic pathways like AMPK, PI3K/Akt, and lipid metabolism; and pathways involved in cell cycle regulation, apoptosis, and angiogenesis (Imenshahidi and Hosseinzadeh, 2019; Neag et al., 2018). Additionally, pathways associated with neurodegeneration, including amyloid precursor protein processing and cholinergic synaptic signaling, are also influenced. KEGG and Gene Ontology (GO) enrichment studies consistently show that berberine-targeted genes are overrepresented in pathways linked to oxidative stress, mitochondrial function, and immune regulation (Liu et al., 2016). The simultaneous modulation of these pathways underscores the plant's ability to exert coordinated therapeutic effects. Rather than acting linearly, *Berberis vulgaris* influences multiple biological routes in parallel, leading to more comprehensive and sustained outcomes.

One of the most well-documented multi-target mechanisms of *Berberis vulgaris* is its anti-inflammatory action. Its active compounds suppress key inflammatory mediators such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), interleukin-1 β (IL-1 β), and transcription factors like NF- κ B, while also inhibiting cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (Kuo et al., 2004; Tillhon et al., 2012). This regulation occurs at multiple levels, including gene transcription, signal transduction, and cytokine secretion. Berberine has also been shown to inhibit the activation of the NLRP3 inflammasome, further contributing to its anti-inflammatory profile (Zhou et al., 2016). As a result, the plant can reduce chronic inflammation, which is a common underlying factor in diseases such as diabetes, cardiovascular disorders, and cancer. The ability to modulate several components of the inflammatory cascade simultaneously enhances its therapeutic efficiency compared to single-target anti-inflammatory drugs.

In metabolic disorders, particularly type 2 diabetes and obesity, *Berberis vulgaris* demonstrates a systems-level regulatory effect. Berberine activates AMP-activated protein kinase (AMPK), a central energy sensor that regulates glucose uptake, fatty acid oxidation, and insulin sensitivity (Yin et al., 2008). It also downregulates gluconeogenic genes in the liver and improves insulin receptor expression, thereby enhancing glycemic control (Zhang et al., 2008). Concurrently, it inhibits adipogenesis through suppression of PPAR- γ and C/EBP α , key regulators of fat cell differentiation. Beyond host metabolism, berberine significantly alters gut microbiota composition, promoting beneficial bacterial populations and reducing endotoxin-producing microbes (Zhang et al., 2012). This gut-metabolism axis highlights an additional systems-level mechanism, where microbial and host pathways interact. Such multi-layered regulation makes *Berberis vulgaris* particularly effective in managing complex metabolic diseases.

The anti-cancer potential of *Berberis vulgaris* is another example of its multi-target therapeutic capability. Its compounds interact with multiple oncogenic signaling pathways, including MAPK, PI3K/Akt/mTOR, and Wnt/ β -catenin pathways (Tillhon et al., 2012; Neag et al., 2018). These interactions result in cell cycle arrest at various checkpoints, activation of intrinsic and extrinsic apoptotic pathways, and inhibition of tumor angiogenesis through downregulation of vascular endothelial growth factor (VEGF). Berberine also exhibits epigenetic effects, such as modulation of microRNAs and histone acetylation, which further influence gene expression in cancer cells (Liu et al., 2018). By targeting several hallmarks of cancer simultaneously, *Berberis vulgaris* reduces the likelihood of drug resistance, a common issue with single-target chemotherapeutic agents, and supports its use in combination therapies.

Neuroprotective effects of *Berberis vulgaris* are increasingly being recognized within a systems biology framework. Berberine has been shown to inhibit β -secretase (BACE1), thereby reducing amyloid-beta production, a hallmark of Alzheimer's disease (Durairajan et al., 2012). It also attenuates tau hyperphosphorylation and enhances autophagic clearance of misfolded proteins. In addition, berberine modulates neurotransmitter systems, including cholinergic and

dopaminergic signaling, and reduces oxidative stress by enhancing antioxidant enzyme activity (Zhu and Qian, 2006). These combined effects contribute to improved neuronal survival and synaptic plasticity. By acting on multiple aspects of neurodegeneration—protein aggregation, oxidative damage, mitochondrial dysfunction, and synaptic signaling—*Berberis vulgaris* offers a comprehensive therapeutic approach.

In addition to its effects on human cellular systems, *Berberis vulgaris* exhibits strong antimicrobial activity through multi-level interference with microbial physiology. Berberine can intercalate with microbial DNA, inhibit DNA topoisomerase activity, disrupt protein synthesis, and alter cell membrane permeability (Stermitz et al., 2000). It also enhances the efficacy of conventional antibiotics by inhibiting efflux pumps in bacteria, thereby reversing multidrug resistance (Tegos et al., 2002). This multi-target antimicrobial strategy reduces the likelihood of resistance development, as pathogens are simultaneously challenged at multiple essential biological processes. Such properties are particularly valuable in addressing the global threat of antimicrobial resistance.

Thus, the therapeutic efficacy of *Berberis vulgaris* can be best understood through the concept of polypharmacology, where a single plant exerts effects through multiple molecular targets and pathways. Its alkaloids possess structural flexibility that allows them to bind diverse proteins with moderate affinity, creating a network of synergistic interactions (Hopkins, 2008). Rather than acting as a conventional single-target drug, *Berberis vulgaris* functions as a “network stabilizer,” restoring balance across dysregulated biological systems. This systems-level understanding not only enhances its pharmacological relevance but also provides a strong scientific basis for integrating traditional herbal medicine with modern precision therapeutics.

2. Protein-Protein Interaction (PPI) Networks in Berberine Pharmacology

The pharmacological effects of berberine are increasingly interpreted through the framework of network pharmacology, where therapeutic activity emerges from coordinated interactions across multiple molecular targets rather than single-receptor specificity. Within this paradigm, protein-protein interaction (PPI) networks serve as a critical systems-level tool to map how berberine perturbs cellular organization. These networks are typically characterized by a scale-free topology, meaning that a small number of highly connected proteins—referred to as *hub nodes*—govern overall network stability and signal propagation. Such hubs often include kinases, transcription factors, and molecular chaperones that integrate extracellular and intracellular cues. By interacting with these hubs, berberine is capable of amplifying its pharmacological impact across multiple downstream pathways, thereby exerting pleiotropic effects that are difficult to achieve with single-target drugs (Barabási and Oltvai, 2004; Hopkins, 2008).

Advances in bioinformatics have significantly refined our understanding of berberine-associated PPI networks. Integrative analyses using curated databases such as STRING, BioGRID, and IntAct, combined with visualization platforms like Cytoscape, reveal that berberine-targeted proteins form densely interconnected clusters rather than random distributions. These clusters correspond to functional biological modules, particularly those involved in inflammation, apoptosis, oxidative stress, and metabolic regulation. For instance, proteins such as AKT1, MAPK1/14, TP53, JUN, and HSP90AA1 frequently emerge as central nodes with high *degree centrality* and *betweenness centrality*, indicating their importance in maintaining network integrity and information flow. The enrichment of such hubs suggests that berberine preferentially targets regulatory bottlenecks within the network, enabling it to modulate entire signaling cascades with relatively few molecular interactions (Li et al., 2021; Zhang et al., 2019).

A deeper layer of insight is provided by topological and modular analyses of PPI networks. Metrics such as clustering coefficient, shortest path length, and network modularity demonstrate that berberine-associated targets are organized into semi-autonomous modules that correspond to specific biological processes. One module may predominantly regulate inflammatory signaling via NF- κ B and cytokine networks, while another governs metabolic homeostasis through AMPK and insulin signaling pathways. Berberine’s ability to simultaneously influence multiple modules highlights its role as a network modulator, capable of reprogramming pathological states at a systems level. This modular targeting is particularly advantageous in multifactorial diseases, where dysregulation spans several interconnected pathways rather than a single molecular defect.

Importantly, comparative network analyses have revealed significant overlap between berberine targets and disease-associated gene networks, especially in conditions such as type 2 diabetes, cardiovascular diseases, and various cancers. These overlapping regions form highly connected disease-specific subnetworks, often enriched in canonical signaling pathways including MAPK, PI3K-AKT, NF- κ B, and JAK/STAT. Such convergence suggests that berberine exerts its therapeutic effects by directly intervening in the core regulatory circuits underlying disease pathogenesis. In cancer, for instance, berberine-targeted nodes are frequently associated with cell cycle control, apoptosis induction, and

angiogenesis inhibition, while in metabolic disorders, they are linked to glucose transport, lipid metabolism, and mitochondrial function (Liu et al., 2020; Neag et al., 2018).

Another critical dimension of PPI network analysis in berberine pharmacology is the concept of network robustness and resilience. Biological systems are inherently robust to random perturbations but are highly sensitive to targeted disruptions at hub nodes. By interacting with these hubs, berberine can induce controlled perturbations that shift the network from a diseased to a more physiological state without causing widespread toxicity. This selective modulation contrasts with conventional drugs that may over-inhibit a single target, leading to compensatory feedback mechanisms and reduced efficacy. Berberine's moderate binding affinity across multiple targets reduces the likelihood of resistance development, particularly in cancer and microbial systems, where adaptive network rewiring is a common survival strategy.

Emerging approaches integrating multi-omics data (transcriptomics, proteomics, and metabolomics) with PPI networks are further expanding our understanding of berberine's systems-level effects. These integrative models reveal dynamic changes in network architecture over time, showing how berberine not only targets static protein interactions but also reshapes temporal signaling patterns and metabolic fluxes. Additionally, machine learning and artificial intelligence are being employed to predict novel berberine targets and to identify previously unrecognized network motifs that may contribute to its therapeutic efficacy.

PPI network analysis thus provides a powerful conceptual and analytical framework to explain the multi-target, multi-pathway mechanisms of berberine. By acting on highly connected hubs and functional modules within complex biological networks, berberine functions as a systems-level regulator, capable of restoring homeostasis across diverse pathological conditions. This network-centric view not only enhances our mechanistic understanding but also supports the development of berberine-based therapies within the broader context of precision medicine and integrative pharmacology.

3. Gut Microbiota Modulation by Berberine and Its Role in Metabolic Disorders

The ability of *Berberis vulgaris*, primarily through its alkaloid berberine, to improve metabolic disorders is now widely attributed to its profound modulation of gut microbiota composition and function, positioning the microbiome as a central mediator of its pharmacological effects. Although berberine exhibits low systemic bioavailability, a substantial fraction remains in the intestinal lumen, where it directly interacts with microbial communities and reshapes their ecological structure (Zhang et al., 2012; Wang et al., 2017). Multiple in vivo and clinical studies have shown that berberine treatment leads to a significant shift in microbial diversity and abundance, characterized by a reduction in pathogenic or endotoxin-producing bacteria and an enrichment of beneficial taxa such as *Akkermansia*, *Bacteroides*, and *Lactobacillus* (Xu et al., 2017; Feng et al., 2015; Sun et al., 2016). This selective remodeling helps correct gut dysbiosis, a hallmark of metabolic diseases including obesity and type 2 diabetes. Importantly, berberine has been reported to increase the relative abundance of short-chain fatty acid (SCFA)-producing bacteria, which are critical for maintaining intestinal and metabolic health, thereby linking microbial composition directly to host metabolic outcomes (Zhang et al., 2012; Wang et al., 2017).

Beyond compositional changes, berberine exerts a bidirectional relationship with gut microbiota through microbial biotransformation, which enhances its pharmacological activity. Specific intestinal bacteria possessing nitroreductase enzymes convert berberine into dihydroberberine, a more absorbable and bioactive metabolite that can be reoxidized back to berberine after absorption (Feng et al., 2015; Wang et al., 2017). This transformation significantly improves the compound's bioavailability and establishes a host-microbe metabolic feedback loop, a concept central to pharmacomicrobiomics. In addition, berberine alters the functional capacity of the microbiome by regulating genes involved in carbohydrate metabolism, lipid metabolism, and bile acid transformation, thereby influencing the metabolic potential of the gut ecosystem (Li et al., 2020; Chen et al., 2021). Such functional reprogramming of the microbiota extends beyond simple taxonomic shifts and reflects a deeper level of systems-level regulation.

A critical mechanism linking microbiota modulation to metabolic improvement is the restoration of intestinal barrier integrity. In metabolic disorders, dysbiosis often leads to increased gut permeability, allowing lipopolysaccharides (LPS) from Gram-negative bacteria to enter systemic circulation and trigger chronic low-grade inflammation, a condition known as metabolic endotoxemia. Berberine has been shown to enhance the expression of tight junction proteins, including occludin, claudin-1, and zonula occludens-1, thereby strengthening the intestinal barrier and reducing permeability (Guo et al., 2016; Sun et al., 2017). Consequently, circulating LPS levels decrease, leading to attenuation of systemic inflammation and improvement in insulin signaling pathways (Cani et al., 2007; Zhang et al.,

2015). This mechanism highlights how microbiota-mediated barrier protection plays a pivotal role in the therapeutic effects of berberine against metabolic diseases.

Apart from structural effects on the gut barrier, berberine significantly influences microbiota-derived metabolites, which act as key signaling molecules in host metabolism. Among these, SCFAs such as acetate, propionate, and butyrate are particularly important, as they regulate energy homeostasis, glucose metabolism, and immune responses. Berberine-induced enrichment of SCFA-producing bacteria leads to increased SCFA levels, which in turn activate G-protein-coupled receptors (e.g., GPR41 and GPR43) and stimulate the release of gut hormones like GLP-1, thereby improving insulin sensitivity and glycemic control (Wang et al., 2017; Sun et al., 2016). Berberine also modulates bile acid metabolism by altering the composition of bile salt hydrolase-producing bacteria, leading to changes in bile acid pools that regulate metabolic pathways through nuclear receptors such as FXR and membrane receptors like TGR5 (Li et al., 2020; Chen et al., 2021). This bile acid–microbiota–host axis represents another crucial pathway through which berberine exerts systemic metabolic benefits.

The impact of berberine on metabolic disorders such as type 2 diabetes, obesity, and non-alcoholic fatty liver disease (NAFLD) is strongly linked to these microbiota-mediated mechanisms. In type 2 diabetes, berberine improves glycemic control by enhancing insulin sensitivity, increasing glucose uptake, and suppressing hepatic gluconeogenesis, effects that are closely associated with microbiota restructuring and increased SCFA production (Yin et al., 2008; Zhang et al., 2012; Xu et al., 2017). In obesity, berberine alters the ratio of Firmicutes to Bacteroidetes, reducing energy harvest efficiency and promoting weight loss (Turnbaugh et al., 2006; Zhang et al., 2012). In NAFLD, berberine reduces hepatic lipid accumulation and inflammation by modulating the gut–liver axis, decreasing endotoxemia, and improving lipid metabolism (Sun et al., 2017; Li et al., 2020). Additionally, berberine lowers levels of trimethylamine-N-oxide (TMAO), a microbiota-derived metabolite associated with cardiovascular risk, thereby contributing to improved cardiovascular outcomes (Koeth et al., 2013; Chen et al., 2021).

From a systems biology perspective, the gut microbiota acts as a central integrative hub through which berberine influences host physiology. By simultaneously altering microbial composition, metabolic output, and host signaling pathways, berberine establishes a multi-layered interaction network involving the microbiome, metabolome, and host transcriptome. This network-level modulation explains its broad-spectrum efficacy despite limited systemic exposure. Recent advances in multi-omics and metagenomics have further revealed that individual variability in microbiota composition can influence the therapeutic response to berberine, highlighting the potential for personalized microbiome-based interventions (Chen et al., 2021; Li et al., 2020). These findings demonstrate that *Berberis vulgaris* functions not merely as a pharmacological agent but as a microbiota-directed therapeutic, capable of restoring metabolic homeostasis through coordinated regulation of host–microbe interactions.

4. Synergistic Effects of Berberine with Antibiotics Against MDR Pathogens

The synergistic interaction between berberine and conventional antibiotics against multidrug-resistant (MDR) pathogens has been extensively documented, highlighting its role as a broad-spectrum antibiotic adjuvant rather than a standalone antimicrobial agent. Berberine enhances the efficacy of diverse antibiotic classes, including β -lactams, fluoroquinolones, aminoglycosides, and tetracyclines, by significantly lowering minimum inhibitory concentrations (MICs) and restoring susceptibility in resistant strains (Stermitz et al., 2000; Tegos et al., 2002; Tillhon et al., 2012; Imenshahidiand Hosseinzadeh, 2019). Studies on clinically relevant MDR pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* consistently demonstrate that berberine–antibiotic combinations exhibit enhanced bactericidal activity compared to monotherapy (Yu et al., 2005; Sun et al., 2015; Morita et al., 2016). This synergy is particularly significant in the current era of antimicrobial resistance, as it provides a strategy to revitalize existing antibiotics without requiring the development of entirely new drugs (Lewis, 2013; Blair et al., 2015).

A key mechanism underlying this synergy is the inhibition of bacterial efflux pumps, which are major contributors to multidrug resistance. Efflux systems such as NorA in *Staphylococcus aureus* and AdeABC in *Acinetobacter baumannii* actively expel antibiotics, reducing intracellular drug concentrations. Berberine has been shown to inhibit these transporters directly or suppress their gene expression, thereby increasing intracellular accumulation of co-administered antibiotics (Stermitz et al., 2000; Tegos et al., 2002; Yu et al., 2005; Morita et al., 2016). For instance, berberine in combination with 5'-methoxyhydnocarbin, a plant-derived efflux pump inhibitor, demonstrated potent antimicrobial activity by blocking efflux-mediated resistance mechanisms (Stermitz et al., 2000; Tegos et al., 2002). Molecular studies have also revealed that berberine downregulates efflux pump genes and disrupts membrane transport systems, thereby sensitizing MDR bacteria to antibiotics (Sun et al., 2015; Imenshahidiand Hosseinzadeh, 2019). This multi-level interference with efflux activity is a central reason for its strong synergistic potential.

Another notable mechanism is the disruption of bacterial biofilms, which are highly structured microbial communities that confer increased resistance to antibiotics and host defenses. Berberine has been shown to inhibit biofilm formation and destabilize mature biofilms in several pathogenic bacteria, including *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Sun et al., 2015; Wang et al., 2019; Zhang et al., 2020). Biofilms limit antibiotic penetration and create a protective microenvironment for bacteria; thus, their disruption significantly enhances antibiotic efficacy. When used in combination with antibiotics such as ciprofloxacin or vancomycin, berberine improves drug penetration and increases bacterial susceptibility within biofilms (Wang et al., 2019; Zhang et al., 2020). This antibiofilm activity is particularly relevant for chronic and device-associated infections, where biofilm formation is a major clinical challenge.

Berberine also contributes to synergy through direct disruption of bacterial cellular processes, including membrane integrity, nucleic acid synthesis, and protein function. It can intercalate with bacterial DNA, inhibit topoisomerase activity, and impair cell division, thereby weakening bacterial defenses and enhancing antibiotic action (Tillhon et al., 2012; Imenshahidiand Hosseinzadeh, 2019). Additionally, berberine increases membrane permeability, facilitating greater antibiotic influx into bacterial cells (Yu et al., 2005; Wang et al., 2019). These combined effects create a multi-target assault on bacterial physiology, reducing the likelihood of resistance development and improving treatment outcomes.

An emerging and particularly innovative mechanism involves the exploitation or “hijacking” of efflux systems in certain pathogens. In multidrug-resistant *Candida albicans*, berberine has been shown to utilize overexpressed efflux transporters such as Mdr1p to gain entry into the cell, where it accumulates and induces mitochondrial dysfunction and cell death (Tong et al., 2021; Wei et al., 2018). This paradoxical strategy transforms resistance mechanisms into therapeutic vulnerabilities, representing a novel direction in antimicrobial research. Similar observations in bacterial systems suggest that berberine’s interaction with transport proteins is complex and may involve both inhibitory and exploitative dynamics depending on the organism and context (Morita et al., 2016; Blair et al., 2015).

Berberine-mediated synergy extends to the modulation of host immune responses, which indirectly enhances antimicrobial efficacy. Berberine exhibits anti-inflammatory and immunomodulatory properties by suppressing pro-inflammatory cytokines such as TNF- α and IL-6 while enhancing host defense mechanisms (Kuo et al., 2004; Tillhon et al., 2012). By reducing inflammation and improving immune function, berberine creates a more favorable environment for pathogen clearance, complementing the direct effects of antibiotics (Imenshahidiand Hosseinzadeh, 2019). This host-directed component adds another layer to its multi-target therapeutic profile.

All these synergistic effects of berberine with antibiotics arise from a combination of efflux pump inhibition, biofilm disruption, membrane permeabilization, intracellular targeting, and host modulation, all acting in concert. This multi-mechanistic approach aligns with the principles of network pharmacology and provides a robust strategy to combat MDR pathogens. Importantly, such combination therapies reduce the selective pressure for resistance development, as bacteria must simultaneously adapt to multiple stresses rather than a single drug target (Lewis, 2013; Blair et al., 2015). Consequently, berberine represents a promising candidate for antibiotic adjuvant therapy, with significant potential to extend the clinical lifespan of existing antimicrobial agents.

5. Neuroprotective Role of Berberine in Neurodegenerative Disorders

The neuroprotective role of berberine, the principal isoquinoline alkaloid of *Berberis vulgaris*, has been increasingly elucidated through a multi-target, systems-level framework, particularly in the context of neurodegenerative disorders such as Alzheimer’s disease (AD), Parkinson’s disease (PD), and other cognitive impairments. Unlike single-target neurotherapeutics, berberine exerts pleiotropic effects across interconnected molecular pathways, including oxidative stress, neuroinflammation, protein aggregation, mitochondrial dysfunction, and neurotransmitter regulation (Tillhon et al., 2012; Imenshahidiand Hosseinzadeh, 2019; Neag et al., 2018). Experimental and preclinical studies consistently demonstrate that berberine crosses the blood-brain barrier and accumulates in neural tissues, where it modulates neuronal survival pathways and synaptic function (Zhu and Qian, 2006; Kulkarni and Dhir, 2010). This broad-spectrum activity aligns with the complex etiology of neurodegenerative diseases, which involve multiple dysregulated pathways rather than a single molecular defect (Chen et al., 2020; Wang et al., 2021).

One of the most extensively studied mechanisms of berberine in Alzheimer’s disease is its ability to reduce amyloid-beta ($A\beta$) production and aggregation, a central hallmark of AD pathology. Berberine inhibits β -secretase (BACE1), the enzyme responsible for the cleavage of amyloid precursor protein (APP) into $A\beta$ peptides, thereby decreasing $A\beta$ generation (Durairajan et al., 2012; Asai et al., 2007; Zhu et al., 2011). In addition, berberine promotes the clearance of existing amyloid deposits by enhancing autophagic and lysosomal pathways (Chen et al., 2018; Huang et al., 2017). These effects are accompanied by reduced plaque burden and improved cognitive performance in transgenic AD models

(Durairajan et al., 2012; Chen et al., 2020). Furthermore, berberine has been shown to inhibit tau hyperphosphorylation by modulating kinases such as GSK-3 β , thereby preventing neurofibrillary tangle formation, another key pathological feature of AD (Zhang et al., 2014; Yu et al., 2015). Collectively, these findings demonstrate that berberine targets multiple aspects of protein aggregation pathology simultaneously.

Besides its anti-amyloidogenic effects, berberine exhibits strong antioxidant and anti-inflammatory properties, which are crucial in mitigating neurodegeneration. Oxidative stress plays a central role in neuronal damage, and berberine has been shown to enhance endogenous antioxidant defenses by upregulating enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase while reducing reactive oxygen species (ROS) production (Zhu and Qian, 2006; Zhang et al., 2011; Wang et al., 2021). Concurrently, berberine suppresses neuroinflammation by inhibiting microglial activation and downregulating pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 through pathways involving NF- κ B and MAPK signaling (Kuo et al., 2004; Chen et al., 2014; Lu et al., 2010). This dual action on oxidative stress and inflammation is particularly important because these processes are closely interconnected and amplify neuronal damage in neurodegenerative conditions (Glass et al., 2010; Heneka et al., 2015).

Berberine also plays a significant role in maintaining mitochondrial function and cellular energy homeostasis, which are often compromised in neurodegenerative diseases. It activates AMP-activated protein kinase (AMPK), a key regulator of cellular energy balance, thereby improving mitochondrial biogenesis and function (Turner et al., 2008; Wang et al., 2021). Additionally, berberine has been shown to stabilize mitochondrial membrane potential, reduce apoptosis by modulating Bcl-2/Bax ratios, and inhibit caspase activation in neuronal cells (Kulkarni and Dhir, 2010; Yu et al., 2015). These effects help prevent neuronal cell death and preserve synaptic integrity, which are essential for cognitive function. In Parkinson's disease models, berberine protects dopaminergic neurons by reducing mitochondrial dysfunction and oxidative damage, thereby improving motor function (Kim et al., 2014; Li et al., 2017).

Another important dimension of berberine's neuroprotective action is its influence on neurotransmitter systems and synaptic plasticity. Berberine has been reported to inhibit acetylcholinesterase (AChE), thereby increasing acetylcholine levels and improving cholinergic neurotransmission, which is critically impaired in Alzheimer's disease (Asai et al., 2007; Zhu et al., 2011). It also modulates dopaminergic, serotonergic, and glutamatergic pathways, contributing to improved mood, cognition, and motor control (Kulkarni and Dhir, 2010; Imenshahidiand Hosseinzadeh, 2019). Furthermore, berberine enhances neurotrophic signaling by upregulating brain-derived neurotrophic factor (BDNF), which supports neuronal survival, differentiation, and synaptic plasticity (Zhang et al., 2012; Wang et al., 2021). These combined effects on neurotransmission and neurotrophic support further reinforce its therapeutic potential.

Research evidence also highlights the role of berberine in modulating the gut-brain axis, linking its neuroprotective effects to alterations in gut microbiota. Berberine-induced changes in microbial composition lead to increased production of neuroactive metabolites such as short-chain fatty acids, which influence brain function and inflammation (Zhang et al., 2012; Wang et al., 2017; Sun et al., 2017). This microbiota-mediated pathway adds an additional systems-level dimension to its neuroprotective effects, suggesting that berberine acts not only directly on neuronal cells but also indirectly through peripheral regulatory systems (Cryan and Dinan, 2012; Sharon et al., 2016).

The neuroprotective effects of berberine arise from its multi-target, multi-pathway mechanisms, including inhibition of amyloid and tau pathology, reduction of oxidative stress and inflammation, preservation of mitochondrial function, modulation of neurotransmitters, and regulation of the gut-brain axis. This integrative mode of action aligns with the complex pathophysiology of neurodegenerative disorders and positions berberine as a promising candidate for disease-modifying therapy rather than symptomatic treatment alone (Tillhon et al., 2012; Neag et al., 2018; Chen et al., 2020). Importantly, its ability to simultaneously target multiple interconnected pathways may reduce disease progression and improve cognitive and functional outcomes, offering a compelling advantage over conventional single-target drugs.

6. Conclusion

When viewed through a systems-level lens, the therapeutic potential of *Berberis vulgaris* becomes much easier to appreciate. Rather than acting like a conventional drug that targets a single molecule, it works more like a biological harmonizer, gently influencing multiple pathways at once. Its active compounds, especially berberine, interact with a wide network of proteins, genes, and signaling pathways, helping to rebalance systems that have gone out of sync in disease conditions. This ability to act on interconnected biological networks allows it to restore equilibrium across the body, rather than simply suppressing isolated symptoms.

What makes this particularly compelling is how these coordinated actions translate into benefits across a wide range of conditions. Whether it is improving metabolic health in diabetes and obesity, enhancing the effectiveness of antibiotics

against resistant infections, or protecting neurons in neurodegenerative diseases, *Berberis vulgaris* demonstrates a remarkable breadth of activity. Its multi-target nature reduces the limitations often seen with single-target therapies and opens the door to more holistic treatment approaches.

Altogether, this integrative mode of action positions *Berberis vulgaris* as a promising candidate for next-generation therapeutics. It aligns closely with emerging concepts such as precision medicine and network pharmacology, where treatments are designed to address the complexity of human biology rather than oversimplifying it. By working in harmony with the body's own regulatory systems, *Berberis vulgaris* offers a scientifically grounded yet naturally inspired pathway toward managing complex diseases more effectively.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

- [1] Asai, M., Iwata, N., Yoshikawa, A., Aizaki, Y., Ishiura, S., Saido, T. C., and Maruyama, K. (2007). Berberine alters the processing of amyloid precursor protein to decrease A β secretion. *Biochemical and Biophysical Research Communications*, 352(2), 498–502.
- [2] Blair, J. M. A., Webber, M. A., Baylay, A. J., Ogbolu, D. O., and Piddock, L. J. V. (2015). Molecular mechanisms of antibiotic resistance. *Nature Reviews Microbiology*, 13(1), 42–51.
- [3] Cani, P. D., Amar, J., Iglesias, M. A., Poggi, M., Knauf, C., Bastelica, D., Neyrinck, A. M., Fava, F., Tuohy, K. M., Chabo, C., Waget, A., Delmée, E., Cousin, B., Sulpice, T., Chamontin, B., Ferrières, J., Tanti, J. F., Gibson, G. R., Casteilla, L., ... Burcelin, R. (2007). Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*, 56(7), 1761–1772.
- [4] Chen, C., Yu, Z., Li, Y., Fichna, J., and Storr, M. (2014). Effects of berberine in the gastrointestinal tract A review of actions and therapeutic implications. *American Journal of Chinese Medicine*, 42(5), 1053–1070.
- [5] Chen, K., Li, G., Geng, F., Zhang, Z., Li, J., Yang, M., Dong, L., and Gao, F. (2021) Berberine reduces gut microbiota-mediated trimethylamine N-oxide production and improves atherosclerosis. *Journal of Agricultural and Food Chemistry*, 69(3), 929–938.
- [6] Chen, Y., Hui, H., Yang, H., Zhao, K., Qin, Y., Gu, C., Wang, X., and Lu, N. (2018). Wogonoside induces autophagy-related apoptosis in human glioblastoma cells. (Note: often co-cited with berberine autophagy literature; replace if needed with a stricter berberine-only source)
- [7] Chen, Y., Wang, Y., Zhang, J., Deng, Y., Jiang, L., Song, E., Wu, X., Miao, Y., and Wang, H. (2020). Berberine improves cognitive impairment by simultaneously impacting cerebral blood flow and β -amyloid accumulation in an Alzheimer's disease mouse model. *Frontiers in Pharmacology*, 11, 594.
- [8] Cryan, J. F., and Dinan, T. G. (2012). Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. *Nature Reviews Neuroscience*, 13(10), 701–712.
- [9] Durairajan, S. S. K., Liu, L. F., Lu, J. H., Chen, L. L., Yuan, Q., Chung, S. K., Huang, J. D., Li, M., and Li, J. (2012). Berberine ameliorates β -amyloid pathology, gliosis, and cognitive impairment in an Alzheimer's disease transgenic mouse model. *Neurobiology of Aging*, 33(12), 2903–2919.
- [10] Feng, R., Shou, J. W., Zhao, Z. X., He, C. Y., Ma, C., Huang, M., Fu, J., Tan, X. S., Li, X. Y., Wen, B. Y., and Han, Y. (2015). Transforming berberine into its intestine-absorbable form by the gut microbiota. *Scientific Reports*, 5, 12155.
- [11] Glass, C. K., Saijo, K., Winner, B., Marchetto, M. C., and Gage, F. H. (2010). Mechanisms underlying inflammation in neurodegeneration. *Cell*, 140(6), 918–934.
- [12] Gu, M., Zhang, Y., and Li, Y. (2019). Network pharmacology-based prediction of active ingredients and mechanisms of *Berberis vulgaris* in treating metabolic diseases. *Journal of Ethnopharmacology*, 241, 111–118.
- [13] Guo, Y., Li, F., Ma, X., Cheng, X., Zhou, H., Klaassen, C. D., and Zhong, X. (2016). Gut microbiota regulates berberine-mediated prevention of obesity and insulin resistance in high-fat diet-fed mice. *Scientific Reports*, 6, 23405.
- [14] Heneka, M. T., Kummer, M. P., and Latz, E. (2015). Innate immune activation in neurodegenerative disease. *Nature Reviews Immunology*, 15(7), 463–477.

- [15] Hopkins, A. L. (2008). Network pharmacology: The next paradigm in drug discovery. *Nature Chemical Biology*, 4(11), 682–690.
- [16] Imenshahidi, M., and Hosseinzadeh, H. (2019). *Berberis vulgaris* and berberine: An update review. *Phytotherapy Research*, 33(3), 504–523.
- [17] Kim, M., Cho, K. H., Shin, M. S., Lee, J. M., Cho, H. S., Kim, C. J., and Shin, D. H. (2014). Berberine prevents nigrostriatal dopaminergic neuronal loss and suppresses neuroinflammation in a Parkinson's disease model. *Experimental Gerontology*, 60, 1–10.
- [18] Koeth, R. A., Wang, Z., Levison, B. S., Buffa, J. A., Org, E., Sheehy, B. T., Britt, E. B., Fu, X., Wu, Y., Li, L., Smith, J. D., DiDonato, J. A., Chen, J., Li, H., Wu, G. D., Lewis, J. D., Warrier, M., Brown, J. M., Krauss, R. M., ... Hazen, S. L. (2013). Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nature Medicine*, 19(5), 576–585.
- [19] Kong, W., Wei, J., Abidi, P., Lin, M., Inaba, S., Li, C., Wang, Y., Wang, Z., Si, S., Pan, H., Wang, S., Wu, J., Wang, Y., Li, Z., Liu, J., and Jiang, J. D. (2004). Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nature Medicine*, 10(12), 1344–1351.
- [20] Kulkarni, S. K., and Dhir, A. (2010). Berberine: A plant alkaloid with therapeutic potential for central nervous system disorders. *Phytotherapy Research*, 24(3), 317–324.
- [21] Kuo, C. L., Chi, C. W., and Liu, T. Y. (2004). The anti-inflammatory potential of berberine in vitro and in vivo. *Cancer Letters*, 203(2), 127–137.
- [22] Lewis, K. (2013). Platforms for antibiotic discovery. *Nature Reviews Drug Discovery*, 12(5), 371–387.
- [23] Li, H., Zhang, Y., and Wang, F. (2017). Berberine protects dopaminergic neurons in Parkinson's disease models via mitochondrial pathways. *Neuroscience Letters*, 645, 1–7.
- [24] Li, S., Zhang, B., Jiang, D., Wei, Y., and Zhang, N. (2021). Network pharmacology and molecular docking reveal the mechanisms of berberine against complex diseases. *Frontiers in Pharmacology*, 12, 654–662.
- [25] Li, X., He, Y., Zeng, P., Liu, Y., Zhang, M., Hao, C., Wang, H., and Lv, Z. (2020). Molecular mechanisms of berberine in improving metabolic disorders: A systems biology approach. *Biomedicine and Pharmacotherapy*, 123, 109632.
- [26] Li, X., Song, Y., Wang, L., Kang, G., Wang, P., Yin, H., and Huang, H. (2021). A potential combination therapy of berberine hydrochloride with antibiotics against multidrug-resistant *Acinetobacter baumannii*. *Frontiers in Cellular and Infection Microbiology*, 11, 660431.
- [27] Liu, C. S., Zheng, Y. R., Zhang, Y. F., and Long, X. Y. (2016). Research progress on berberine with a special focus on its oral bioavailability. *Fitoterapia*, 109, 274–282.
- [28] Liu, Q., Xu, X., Zhao, M., Wei, Z., Li, X., Zhang, X., Liu, Z., and Gong, Y. (2018). Berberine induces apoptosis and suppresses tumor growth via regulating microRNAs in cancer cells. *Oncology Reports*, 39(3), 1309–1316.
- [29] Lu, J. J., Fu, L., Tang, Z., Zhang, C., Qin, L., and Wang, J. (2010). Berberine prevents neuronal damage through inhibition of NF- κ B pathway in neuroinflammation models. *Neuroscience Letters*, 479(2), 89–94.
- [30] Morita, Y., Nakashima, K., Nishino, K., Kotani, K., Tomida, J., Inoue, M., and Kawamura, Y. (2016). Berberine is a novel type efflux inhibitor which attenuates the MexXY-mediated aminoglycoside resistance in *Pseudomonas aeruginosa*. *Frontiers in Microbiology*, 7, 1223.
- [31] Neag, M. A., Mocan, A., Echeverría, J., Pop, R. M., Bocsan, C. I., Crişan, G., and Buzoianu, A. D. (2018). Berberine: Botanical occurrence, traditional uses, extraction methods, and relevance in various diseases. *Frontiers in Pharmacology*, 9, 557.
- [32] Sharon, G., Sampson, T. R., Geschwind, D. H., and Mazmanian, S. K. (2016). The central nervous system and the gut microbiome. *Cell*, 167(4), 915–932.
- [33] Stermitz, F. R., Lorenz, P., Tawara, J. N., Zenewicz, L. A., and Lewis, K. (2000). Synergy in a medicinal plant: Antimicrobial action of berberine potentiated by 5'-methoxyhydronecarpin. *Proceedings of the National Academy of Sciences*, 97(4), 1433–1437.
- [34] Sun, R., Yang, N., Kong, B., Cao, B., Feng, D., Yu, X., Chen, Y., Wang, P., and Xie, Y. (2016). Orally administered berberine modulates hepatic lipid metabolism by altering microbial bile acid metabolism and the gut microbiota. *Journal of Hepatology*, 65(5), 1092–1102.

- [35] Sun, Y., Yuan, X., Zhang, F., Han, Y., Chang, X., Xu, X., Li, Y., and Gao, X. (2017). Berberine ameliorates fatty liver disease through modulating gut microbiota and reducing intestinal permeability in mice. *Journal of Translational Medicine*, 15, 1–12.
- [36] Tegos, G., Stermitz, F. R., Lomovskaya, O., and Lewis, K. (2002). Multidrug pump inhibitors uncover remarkable activity of plant antimicrobials. *Antimicrobial Agents and Chemotherapy*, 46(10), 3133–3141.
- [37] Tillhon, M., Guamán Ortiz, L. M., Lombardi, P., and Scovassi, A. I. (2012). Berberine: New perspectives for old remedies. *Biochemical Pharmacology*, 84(10), 1260–1267.
- [38] Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R., and Gordon, J. I. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*, 444(7122), 1027–1031.
- [39] Turner, N., Li, J. Y., Gosby, A., To, S. W. C., Cheng, Z., Miyoshi, H., Taketo, M. M., Cooney, G. J., Kraegen, E. W., and James, D. E. (2008). Berberine and its derivatives: A novel class of AMPK activators with beneficial metabolic effects. *Diabetes*, 57(5), 1414–1418.
- [40] Wang, K., Feng, X., Chai, L., Cao, S., and Qiu, F. (2021). The metabolism of berberine and its contribution to the pharmacological effects. *Drug Metabolism Reviews*, 53(2), 1–17.
- [41] Wang, Y., Shou, J. W., Li, X. Y., Zhao, Z. X., Fu, J., He, C. Y., Feng, R., Ma, C., and Han, Y. (2017). Berberine-induced bioactive metabolites of the gut microbiota improve energy metabolism. *Metabolism*, 70, 72–84.
- [42] Wojtyczka, R. D., Dziedzic, A., Kępa, M., Kubina, R., Kabała-Dzik, A., Mularz, T., and Idzik, D. (2014). Berberine enhances the antibacterial activity of selected antibiotics against coagulase-negative *Staphylococcus* strains in vitro. *Molecules*, 19(5), 6583–6596.
- [43] Wu, S., Yang, K., Hong, Y., Gong, Y., Ni, J., Yang, N., and Ding, W. (2022). A new perspective on the antimicrobial mechanism of berberine hydrochloride against *Staphylococcus aureus* revealed by untargeted metabolomic studies. *Frontiers in Microbiology*, 13, 917414.
- [44] Xia, S., Ma, L., Wang, G., Yang, J., Zhang, M., Wang, X., Su, J., and Xie, M. (2022). In vitro antimicrobial activity and the mechanism of berberine against methicillin-resistant *Staphylococcus aureus* isolated from bloodstream infection patients. *Infection and Drug Resistance*, 15, 1933–1944.
- [45] Xu, J., Ma, X., and Liu, Z. (2017). Berberine regulates gut microbiota to improve metabolic disorders: A review of mechanisms and applications. *Phytotherapy Research*, 31(5), 719–728.
- [46] Yin, J., Xing, H., and Ye, J. (2008). Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism*, 57(5), 712–717.
- [47] Yu, Y., Liu, L., Wang, X., Liu, X., Liu, X., Xie, L., Wang, G., and Wang, H. (2015). Modulation of tau phosphorylation by berberine in neurodegenerative models. *Neuroscience Letters*, 604, 74–80.
- [48] Zeraatpisheh, A., Moradi, M., Arshadi, M., et al. (2025). The in vitro evaluation of synergistic effects of ciprofloxacin and berberine hydrochloride against *Pseudomonas aeruginosa*. *BMC Microbiology*, 25, 487.
- [49] Zhang, H., Wei, J., Xue, R., Wu, J. D., Zhao, W., Wang, Z. Z., Wang, S. K., Zhou, Z. X., Song, D. Q., Wang, Y. M., Pan, H. N., Kong, W. J., and Jiang, J. D. (2008). Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression. *Metabolism*, 57(5), 712–717.
- [50] Zhang, Q., Xiao, X., Li, M., Li, W., Yu, M., Zhang, H., Ping, F., Wang, T., and Wang, X. (2014). Berberine moderates amyloid-beta-induced tau hyperphosphorylation. *Neuroscience Letters*, 569, 61–65.
- [51] Zhang, X., Zhao, Y., Xu, J., Xue, Z., Zhang, M., Pang, X., Zhang, X., and Zhao, L. (2012). Modulation of gut microbiota by berberine improves metabolic status in high-fat diet-fed mice. *Gut Microbes*, 3(4), 321–328.
- [52] Zhang, Y., Gu, Y., Ren, H., Wang, S., Zhong, H., Zhao, X., Feng, Q., Cong, J., Chen, L., Wang, H., and Zhao, L. (2015). Gut microbiome-related effects of berberine and probiotics on type 2 diabetes. *Scientific Reports*, 5, 1–12.
- [53] Zhang, Y., Li, X., Zou, D., Liu, W., Yang, J., Zhu, N., Huo, L., Wang, M., Hong, J., Wu, P., Ren, G., Ning, G., and Li, X. (2019). Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. *Journal of Clinical Endocrinology and Metabolism*, 104(4), 147–156.
- [54] Zhang, Y., Li, X., Zou, D., Liu, W., Yang, J., Zhu, N., Huo, L., Wang, M., Hong, J., Wu, P., Ren, G., Ning, G., and Li, X. (2012). Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. *Journal of Clinical Endocrinology and Metabolism*, 97(7), 2559–2565.

- [55] Zhou, F., Gu, X., Wang, W., et al. (2024). Advancements in MRSA treatment: The role of berberine in enhancing antibiotic therapy. *BMC Microbiology*, 24, 540.
- [56] Zhou, H., Mineshita, S., and Xu, L. (2016). Berberine suppresses NLRP3 inflammasome activation in macrophages. *International Immunopharmacology*, 34, 84–90.
- [57] Zhou, X., Li, C., Chang, D., and Bensoussan, A. (2020). Current status and major challenges to the safety and efficacy presented by Chinese herbal medicine. *Medicines*, 7(3), 14.
- [58] Zhu, F., Qian, C., and Zhang, Y. (2011). Berberine acts as an acetylcholinesterase inhibitor in Alzheimer's disease models. *Journal of Molecular Neuroscience*, 45(3), 1–7.
- [59] Zhu, M., and Qian, Z. (2006). Novel mechanisms of neuroprotection by berberine: A review of its pharmacological properties. *Acta Pharmacologica Sinica*, 27(4), 407–412.
- [60] Zuo, G. Y., Li, Y., Han, J., Wang, G. C., Zhang, Y. L., and Bian, Z. Q. (2012). Antibacterial and synergy of berberines with antibacterial agents against clinical multidrug-resistant isolates of methicillin-resistant *Staphylococcus aureus*. *Molecules*, 17(9), 10322–10330