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Literature Review: Insights about Berberine

Zhuowei Li[1*], Ruolin Han[2], Jingran Gao[3]

[1]Chengdu Shude High School, Chengdu, China
[2]Shanghai Weiyu International School, Shanghai, China
[3]YIWU International Academy, Yiwu, China
**Corresponding Author. Email: 2254531457@qq.com*

Abstract. This review summarizes the core advantages and limitations of berberine, a naturally derived alkaloid, around three key aspects: synthesis, mechanism of action, and application. In synthesis, its strength lies in mature natural extraction processes that support stable and low-cost production, while its limitation stems from difficult chemical synthesis and reliance on plant sources that bring sustainability concerns. In terms of mechanism, berberine shows value in multi-target regulation that enables diverse therapeutic effects, yet its efficacy is restricted by poor oral bioavailability that requires higher doses. In application, it demonstrates potential in managing metabolic disorders, infections, and inflammatory conditions, but is accompanied by common side effects, drug interaction risks, and insufficient long-term research data.

Keywords: Berberine, Biosynthesis, DNA intercalation, Bioavailability, Metabolic disorders

1. Introduction

Berberine (chemical formula: $C_{20}H_{18}NO_4^+$) is a benzylisoquinoline alkaloid found in several plants, most notably in the roots, rhizomes, and bark of Berberis (barberry), Coptis (goldthread), and Hydrastis canadensis (goldenseal). The compound was first isolated in the early 19th century, with its therapeutic properties being used in Traditional Chinese Medicine and Ayurvedic practices for over two millennia [1,2]. Berberine has a yellow crystalline solid appearance and is known for its diverse biological effects, including its ability to regulate blood sugar, lower cholesterol, and fight infections (Figure 1, 2).

Historically, berberine was used to treat a variety of ailments, including digestive disorders, infections, and inflammatory conditions. In the modern era, it has gained significant attention in medical research due to its effectiveness in managing type 2 diabetes, hyperlipidemia, and microbial infections. It works through several mechanisms, such as activating AMP-activated protein kinase (AMPK) to regulate metabolic processes, inhibiting enzymes involved in cholesterol synthesis, and interfering with DNA replication in pathogens.

Berberine's unique structural features, including its planar ring system and quaternary nitrogen, allow it to interact with a range of biological molecules, making it an important subject of pharmacological studies [3].

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Figure 1. Dry coptis chinensis

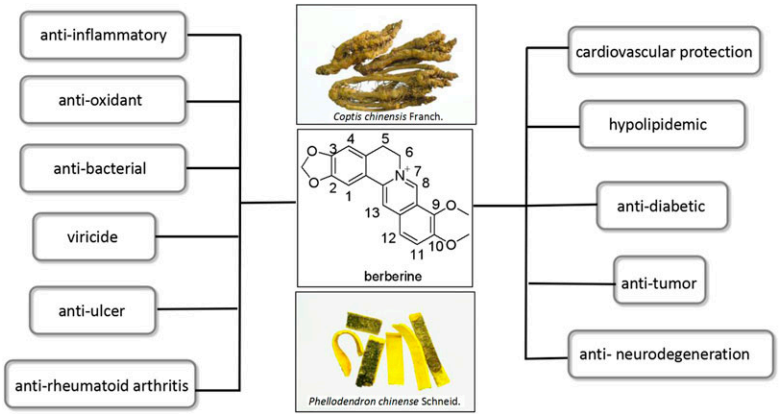

Figure 2. Pharmacological activities of BBR

2. Structure of berberine

For its structure, Berberine is a tetracyclic alkaloid, and the core structure consists of a benzodioxole group along with a quaternary isoquinolinium core.

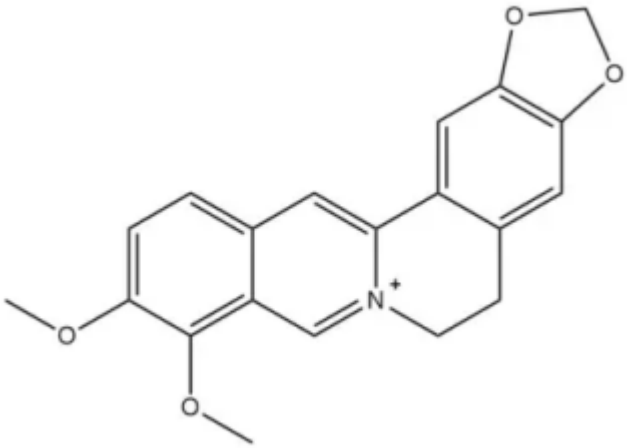

Figure 3. 2D molecular structure

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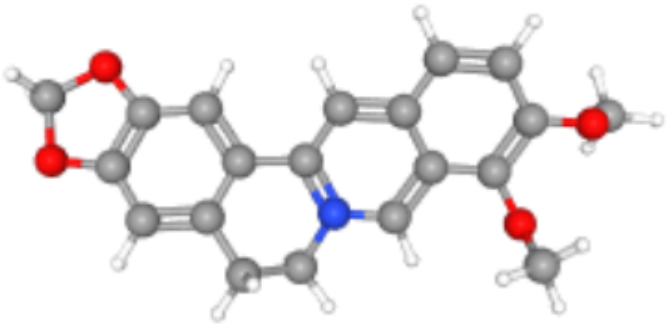

Figure 4. 3D structure

For hybridization, the nitrogen atom, which is in the quaternary ammonium form, is sp^3 hybridized. Aromatic carbons within the molecule are sp^2 hybridized, while methyl groups are also sp^3 hybridized. π - conjugation extends across the entire aromatic core, and this leads to the molecule having a planar structure. This planarity is crucial as it facilitates DNA intercalation. In terms of charge, berberine features a quaternary ammonium group with a positive nitrogen ion (N^+), making the core structure cationic and giving the molecule an overall positive charge. In terms of functional groups, berberine contains methylenedioxy groups, a quaternary ammonium group (N^+), and aromatic ether groups (Figure 3, 4).

3. Biosynthesis of berberine

Berberine is mainly derived from Coptis, Berberis vulgaris and other plants of the Berberis family. Its extraction depends on the physicochemical properties of alkaloids. Since berberine is a weakly basic compound, it can usually be converted into a salt form that is easily soluble in water under acidic conditions. Therefore, acidic solutions are often used to extract the plant powder. Subsequently, by adjusting the pH of the solution, berberine is precipitated in its free base form. Then, impurities are removed and purification is achieved through methods, such as organic solvent extraction or chromatographic separation. In general, the core of this process lies in utilizing the differences in solubility of berberine in different acidic and alkaline environments to effectively separate and enrich it from the natural raw materials.

3.1. Pre-cyclization modification

The synthesis of the core of tetrahydroisoquinoline is a crucial step in the formation process of dopamine derivatives, involving multiple catalytic reactions and stereoselective control. First, tyrosine is converted into dopamine through the action of dopa decarboxylase [4]. Then, dopamine participates in a condensation reaction with 4-hydroxyphenylacetaldehyde. During this process, the aldehyde group undergoes a condensation reaction with the amino group and generates an imine cation intermediate, which exhibits high electrophilicity. The carbon atom of the imine due to its strong negative charge becomes the center for nucleophilic attack.

The formation of the imine cation intermediate is the key step in this reaction process. It not only provides the necessary electrophilic environment for the cyclization reaction which forms a ring structure where functional groups on the molecule react with each other to create a cyclic product [5], of the tetrahydroisoquinoline skeleton, but also lays the foundation for the subsequent

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intramolecular reaction, which means a chemical reaction that occurs inside the molecule itself [6]. The aromatic ring of dopamine is enhanced in electron density because of hydroxyl and methoxy groups. These electron-donating groups significantly increase the electron density of the aromatic ring through the +M effect, making it a highly nucleophilic reactant.

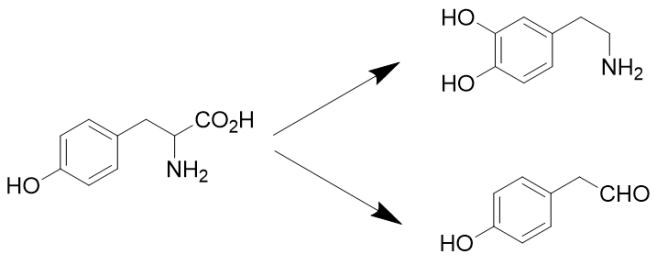

Figure 5. Tyrosine-dopamine

As Figure 5 shows, this electron-rich aromatic ring attacks the carbon atom of the imine cation intermediate through an intramolecular reaction, thereby undergoing a cyclization reaction and ultimately generating the core skeleton of tetrahydroisoquinoline, the (S)-norcocaine alkaloid [7]. The stereoselectivity of this cyclization reaction is regulated by the norcocaine alkaloid synthase. The norcocaine alkaloid synthase enzyme can only generate the S-enantiomer through the correct arrangement of the substrate and the stabilization of the transition state, achieving high stereoselectivity4.

After the tetrahydroisoquinoline skeleton is generated, the hydroxyl group on the aromatic ring is methylated by SAM-dependent O-methyltransferase4, forming methoxy group. This step increases the electron density of the molecule through methylation and alters the spatial configuration of the molecule, enhancing the stability of the aromatic ring (Figure 6).

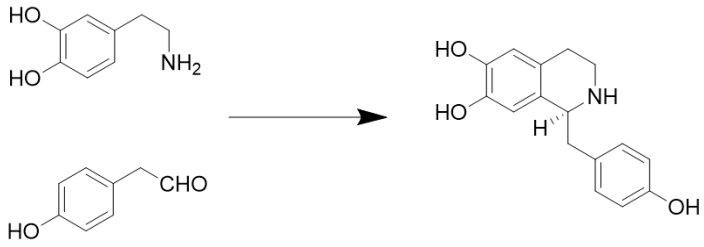

Figure 6. Dopamine-norcoclaurine

As Figure 6 shows, the generated tertiary amine structure may undergo methylation under the catalysis of caffeine N-methyltransferase, further regulating the electronic properties of the molecule and providing the necessary reaction sites for the subsequent oxidation coupling reaction.

The key role of these steps provides important stereoscopic and electronic markers for subsequent reactions by increasing the electron density of the molecules and reducing hydrogen bonding. These methylation steps play a significant role in the reaction process. They not only determine the regioselectivity of the molecule in the oxidation reaction, but also build the chemical foundation for the ring formation reaction of the tetrahydroisoquinoline core. By controlling the sequence of these methylation and oxidation steps, the regioselectivity of the reaction can be effectively regulated, achieving the regulation of specific chemical properties and promoting the further optimization of biological activity.

DOI: 10.54254/2755-2721/2026.KA30852

3.2. Formation of berberine bridge

During the synthesis, the oxidation reaction is essential in the formation of the "berberine bridge". This process is catalyzed by flavin-dependent oxidase, which is berberine bridge enzyme. The berberine bridge enzyme can oxidize the N-methyl or meta-carbon atom of (S)-reticuline berberine and generate a highly electrophilic intermediate4. This reaction is a nucleophilic attack process within the molecule and involves electron transfer and the activation of the aromatic ring. When the highly electrophilic intermediate is formed, the activated aromatic ring attacks the electrophilic carbon atom of the intermediate through the internal nucleophilic attack and forms a new carbon-carbon bond, a unique "berberine bridge" structure. This reaction also promotes the formation of (S)-scoulerine.

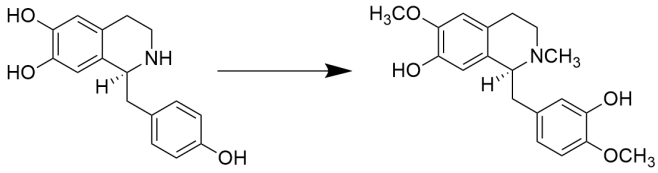

Figure 7. Reticulune-scoulerine

As Figure 7 shows, Flavin adenine dinucleotide acts as a cofactor and stabilizes the intermediate radical through electron transfer, improving the efficiency and selectivity of the reaction.

The sequence and mechanism of this oxidation reaction have been studied through methods like isotope labeling [8], indicating that the oxidation reaction occurs before the ring formation reaction. The flavin adenine dinucleotide cofactor stabilizes the radical intermediates through electron transfer and ensures the accuracy and efficiency of the reaction. The oxidation reaction not only affects the electronic structure of the molecule but also provides a suitable reaction site for the subsequent ring formation reaction, further promoting the synthesis of berberine.

As the reaction progresses, the molecule undergoes a series of further oxidation modification reactions.

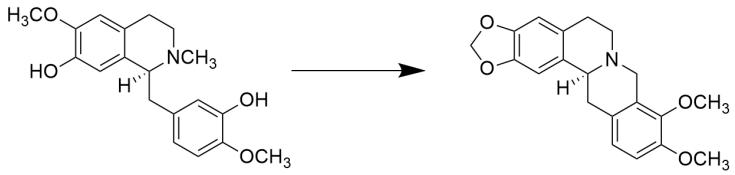

Figure 8. Scoulerine-berberine

Figure 8 shows the transformation from scoulerine to berberine. First, methyltransferases and cytochrome P450 enzymes catalyze the formation of the methylene oxygen bridge on the molecules and complete other oxidation reactions. These reactions can provide assistance for the subsequent structural stability and enable the molecules to transform from the cyclic structure to the bioactive berberine. Cytochrome P450 enzymes mediate these reactions through reactive oxygen species, achieving precise hydroxylation and ring formation reactions [9]. This step not only builds the foundation for the aromatization and electron stability of the final product but also lead to the final transformation of the molecule into the bioactive tetrahydro berberine.

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Ultimately, the molecule undergoes dehydrogenation and aromatization reactions, converting the tetrahydro framework into a fully aromatic quinoline cation with a quaternary ammonium group.

4. Mechanistic basis of berberine's biological activity

Berberine (BBR) exerts its diverse pharmacological functions through three primary molecular mechanisms: DNA binding, membrane interaction, and redox chemistry. These mechanisms, which are not mutually exclusive, collectively account for its antimicrobial, anticancer, anti-inflammatory, and metabolic regulatory activities. In this section, we provide a detailed review of these mechanisms, integrating spectroscopic, structural, and electrochemical evidence from recent investigations.

4.1. DNA binding properties

Berberine possesses a planar rigid, tetracyclic aromatic scaffold, with a positively charged quaternary ammonium nitrogen. Hence, the structural features berberine an archetypal DNA-binding molecule. These two properties — planarity and cationic nature — lead to its interactions with DNA via three principal modes (Figure 9):

Figure 9. RNA duplex with a cytosine bulge in complex with berberine

4.1.1. Intercalation

Berberine can readily slides between adjacent base pairs of DNAs, stabilized by π–π stacking interactions. This binding mode elongates the helix and induces local unwinding.

The molecular spectroscopy evidence of berberine binding to DNA [10] have provided clear evidence for this intercalative binding property. Ultraviolet-visible (UV-vis) spectroscopy revealed characteristic changes: hypochromism (decrease in absorption intensity) and a red shift (shift to longer wavelengths). These effects occur because berberine's π-electron system can interact with and insert between the DNA bases, forming an extended conjugated system. This stacking restricts the movement of π-electrons, reducing the probability of electronic transitions (which causes hypochromism) and decreasing the energy required for those transitions (which leads to red shift).

Additionally, fluorescence spectroscopy showed a significant increase in fluorescence intensity upon binding. This enhancement occurs because intercalation places berberine within the hydrophobic environment between DNA base pairs, which shields it from polar water molecules.

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This protective binding site reduces solvent-induced quenching—a process where collisions with water normally dissipate excited-state energy as heat rather than light. The confined space also limits molecular vibrations and rotations of berberine, further promoting fluorescent emission instead of non-radiative energy loss.

The strength of this interaction was quantified by a binding constant in the order of 10^4 $L \cdot mol^{-1}$, indicating a high affinity between berberine and DNA. A binding constant of this magnitude implies that a significant proportion of berberine would bond to DNA at the equilibrium.

4.1.2. Groove binding

Berberine can also occupy the major or minor grooves of the DNA helix. In this binding mode, the molecule does not insert between base pairs but instead nestles into the grooves, where they can form specific interactions (primarily hydrogen bonds) between molecules with the edges of the nucleobases and the sugar-phosphate backbone. Groove binding is significantly less disruptive to the DNA structure than intercalation. This is because it does not forcibly separate the base pairs or alter local helical parameters by twist and rise. Instead, it involves a more superficial, external association that causes minimal structural distortion. While less disruptive, groove binding is able to bind selectivity, as the ligand can recognize and prefer specific sequences based on the unique pattern of hydrogen bond donors, acceptors, and steric contours presented by the grooves of different nucleotide sequences.

4.1.3. Electrostatic binding

Berberine's cationic charge enables strong attraction to the negatively charged phosphate backbone of DNA. This electrostatic enrichment enhances the local concentration of berberine near nucleic acids, thereby stabilizing intercalated or groove-bound complexes.

4.1.4. Thermodynamics and cooperative binding

Berberine–DNA binding is not a simple one-to-one interaction; instead, it exhibits cooperativity.

Bhadra et. al. [11] revealed the mechanism by which the natural compound berberine interacts with DNA. The research found that this binding is cooperative, meaning that after the first berberine molecule binds to DNA, it would create more favorable conditions for subsequent molecules to bind. This "teamwork" effect is particularly pronounced in GC-rich regions (areas which are abundant in guanine and cytosine).

Researchers used isothermal titration calorimetry (ITC) to precisely measure the energy changes during the binding process and discovered that the driving force stems from the synergistic effects of enthalpy (ΔH) and entropy (ΔS). The enthalpic contribution arises from the energy released during binding. Simultaneously, the entropic effect plays role during binding: the water molecules that were originally orderly arranged on the surfaces of DNA ,and berberine are released into the freely moving solution (desolation), the embedding of berberine's hydrophobic part into the hydrophobic core of DNA as well as the hydrophobic effect, collectively driving the binding process.

4.1.5. Interaction with non-canonical DNA structures

Berberine can interact with non-canonical DNA structures, such as G-quadruplexes (G4), which are four-stranded nucleic acid architectures formed in guanine-rich regions(Mostafavi et.al) [12]. This demonstrated that berberine can stablize human telomeric G-quadruplexes. Notably, berberine

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exhibited higher affinity for hybrid-type G4 structures than parallel ones, indicating its structural selectivity. Such stabilization is biologically significant because it can inhibit telomerase, an enzyme that maintains telomere length in cancer cells, thereby potentially suppressing tumor cell immortalization.

Further structural insight comes from a 2021 NMR study [13] focusing on the parallel MYC G-quadruplex, an important oncogene regulator. The research revealed a novel "base-recruiting" binding mode: berberine does not intercalate in a conventional way but instead captures and positions an external nitrogenous base from the flanking region to assist its own stacking onto the G4-tetrad. This monomeric recognition mechanism differs from earlier crystal structure models.

4.1.6. Biological relevance

Berberine's antimicrobial activity stems primarily from intercalating into bacterial DNA, disrupting replication and transcription processes, and thereby inhibiting bacterial growth. This mechanism is similar to that of classical DNA-targeting antibiotics such as actinomycin D and doxorubicin.

In anticancer applications, berberine targets non-canonical DNA structures in mammalian cells, notably stabilizing G-quadruplexes (G4) in promoter regions of key oncogenes (e.g., MYC, TERT). This impedes transcriptional activity and telomerase function, leading to antiproliferative and pro-apoptotic outcomes. Other small molecules such as CX-5461 (a G4-stabilizing experimental drug) and pyrido statin also operate through G4 interaction, highlighting the therapeutic potential of this mechanism. Unlike conventional chemotherapeutics such as cisplatin, which directly cause DNA cross-linking, berberine offers an alternative mode of genetic regulation that is increasingly regarded as a promising strategy in oncology (Figure 10).

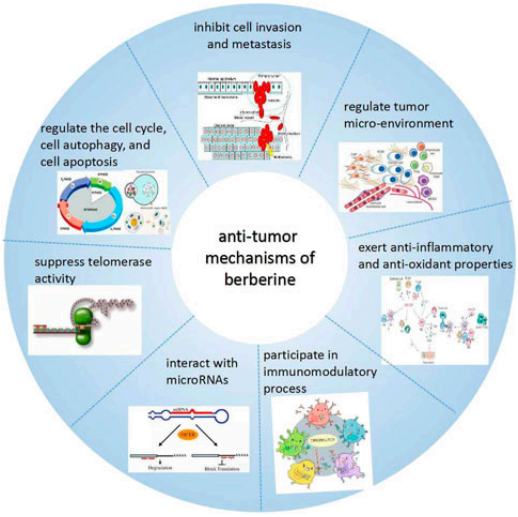

Figure 10. The anti-tumor mechanisms of BBR

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4.2. Membrane interactions

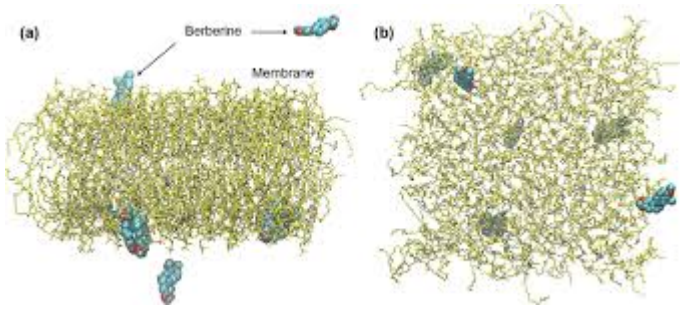

Figure 11. Membrane interaction of berberine

4.2.1. Driving forces and mechanistic basis

In addition to nucleic acids, berberine interacts strongly with biological membranes. This behavior is governed by electrostatics and amphiphilicity (Figure 11):

4.2.2. Electrostatic attraction

Many bacterial and mitochondrial membranes contain negatively charged lipids (e.g., phosphatidylglycerol). Berberine's permanent cationic charge allows it to accumulate at membrane surfaces through Coulombic attraction.

4.2.3. Membrane perturbation

Once inserted, berberine would disrupt lipid packing of membrane, increases membrane permeability, and may create transient pores. This perturbation can depolarize membranes or cause leakage of intracellular contents, leading to cytotoxic effects.

4.2.4. Experimental evidence

Dhakal et. al. [14] investigated how berberine interacts with liposomes—synthetic lipid vesicles used as cellular membrane models—by examining its distribution across membranes of varying lipid compositions. The researchers found that berberine primarily localizes in the aqueous inner core of neutral liposomes, confirms that electrostatic interactions between the positively charged berberine and negatively charged lipids dominate its localization behavior. Consequently, these electrostatic forces also influence berberine's release kinetics—that is, the rate and extent at which the drug is released from the liposome under physiological conditions.

Complementary biophysical techniques, including fluorescence spectroscopy and partition coefficient measurements, further demonstrated that berberine preferentially incorporates into negatively charged bilayers. It can interact with lipid headgroups and acyl chains, which can increase membrane rigidity and reduce bilayer fluidity. These changes in physical properties may affect membrane's normal function and contribute to berberine's biological effects (Figure 12).

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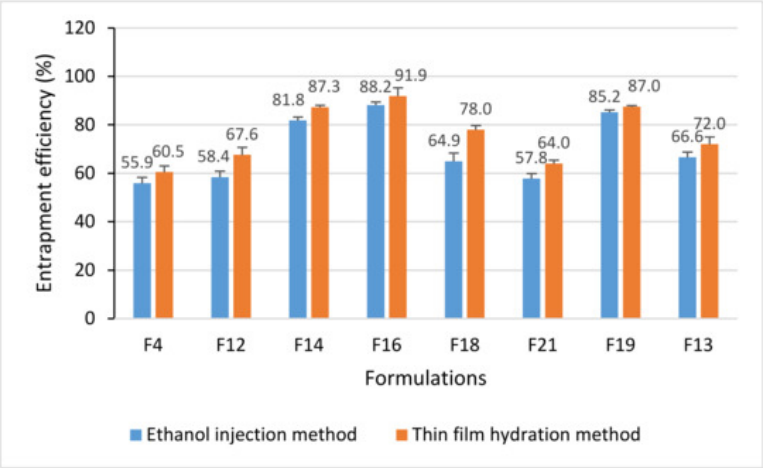

Figure 12. Entrapment efficiency (EE) of the berberine (BBR)-loaded liposomes generated by ethanol-injection (FJ) and thin-film hydration (FH) methods (n = 3, mean ± SD)

4.3. Redox chemistry

Berberine displays complex redox behavior, acting either as an antioxidant or a pro-oxidant.The behavior depends on concentration, cellular context, and the presence of metal ions.

4.3.1. Indirect ROS modulation via mitochondria

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen, such as superoxide ($O_2 \cdot^-$) and hydrogen peroxide (H_2O_2), which can cause oxidative damage or act as signaling molecules. Berberine can increase ROS levels indirectly by targeting to mitochondrial function. It inhibits Complex I of the electron transport chain, leading to electron leakage and increased superoxide production. This elevated oxidative stress promotes apoptosis in cancer cells, while in microbes it contributes to antimicrobial activity.

4.3.2. Direct metal-dependent redox reactions

Berberine can also directly influence redox reactions, especially in the presence of transition metals like iron or copper. When it chelates these metals in a redox-inactive form, it acts as an antioxidant by inhibiting Fenton chemistry, which prevents the formation of harmful hydroxyl radicals (·OH). In contrast, O-demethylated metabolites of berberine (e.g., berberrubine) can reduce Fe^{3+} to Fe^{2+}, accelerating Fenton reactions and increasing ·OH generation, thereby exerting pro-oxidant effects.

4.3.3. Electrochemical studies

Skopalová et. al. [15] investigated the redox properties of berberine using cyclic voltammetry—an electrochemical technique that measures current under varying voltage to identify oxidation and reduction potentials. The researchers analyzed how berberine oxidizes at different pH levels and used mass spectrometry to characterize the resulting oxidation products. They identified a major oxidized metabolite: the demethyleneberberine cation, formed through the loss of a methylene group ($–CH_2–$) from the parent compound. This result demonstrates that oxidation significantly alters berberine's chemical structure, generating diverse metabolites with potentially distinct biological

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activities. The study provides direct electrochemical evidence for berberine's redox reactivity, which helps explain its dual behavior as both an antioxidant and a pro-oxidant depending on the cellular environment.

4.3.4. Biological relevance

Berberine exhibits context-dependent redox activity that contributes to its therapeutic effects. As an antioxidant, it helps protect cells from oxidative damage, thereby reducing inflammation and improving metabolic function. This protective mechanism is similar to that of known antioxidants such as metformin, used in diabetes management, and N-acetylcysteine (NAC), often employed to mitigate oxidative stress. In its pro-oxidant role, berberine promotes the accumulation of reactive oxygen species (ROS), enhancing cytotoxicity against cancer cells and strengthening antimicrobial activity against pathogens. This ROS-mediated mechanism is shared with certain chemotherapeutic agents like artemisinin, which also acts through oxidative damage to induce cancer cell death, and with the antibacterial drug ciprofloxacin, which partly depends on oxidative stress to kill bacteria. The dual redox functionality allows berberine to function both as a cytoprotective agent and a cytotoxic compound, broadening its potential applications in treating metabolic diseases, infections, and cancers.

5. Evaluation

Table 1. Advantages

Synthesis	Berberine is mainly extracted from natural plants (e.g., Berberis vulgaris, Coptis chinensis), with mature industrial extraction protocols. This natural extraction avoids the high cost and environmental risks of complex chemical synthesis, ensuring a stable and low-cost supply [16].
Mechanism	It exerts multi-target regulation, enabling broad therapeutic potential. It activates AMPK (a key energy metabolism regulator) to enhance insulin sensitivity and reduce hyperglycemia [17]; modulates gut microbiota (e.g., increases Akkermansia muciniphila) to alleviate inflammation and metabolic disorders [18]; and inhibits bacterial enzymes (e.g., DNA gyrase) and disrupts microbial cell membranes, showing broad-spectrum antibacterial activity against pathogens like E. coli and Staphylococcus aureus [19].
Application	Metabolic diseases: An RCT found berberine (500 mg thrice daily) reduced HbA1c by 0.7% in type 2 diabetes patients, comparable to metformin [20]; it also lowers LDL-cholesterol by inhibiting hepatic cholesterol synthesis [21]. Infections: It is used topically for bacterial skin infections (e.g., folliculitis) and orally for gastrointestinal infections (e.g., bacterial dysentery) due to its antibacterial properties [19]. Inflammation: It suppresses pro-inflammatory cytokines (e.g., TNF-α, IL-6) by inhibiting the NF-κB pathway, relieving rheumatoid arthritis symptoms [22].

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Table 2. Disadvantages

Synthesis	Chemical synthesis of berberine is difficult due to its complex isoquinoline alkaloid structure. Current routes require 6–8 steps, use expensive reagents (e.g., palladium catalysts), and have a yield of only 15–25%, making large-scale synthetic production economically unfeasible [16]. Dependence on plant sources also faces risks: climate change and over-harvesting threaten the sustainability of raw material supply [23].
Mechanism	Low oral bioavailability (<5%) limits its clinical efficacy. This is due to poor water solubility and intestinal absorption (it is a BCS Class IV drug) [17], as well as extensive first-pass metabolism in the liver (via CYP3A4) and efflux by intestinal transporters (e.g., P-glycoprotein), which reduce systemic exposure [24]. High doses (1–2 g/day) are needed to reach therapeutic concentrations, increasing side effect risks [9].
Application	Side effects: Gastrointestinal disturbances (20–30% of users) such as nausea, diarrhea, abdominal pain, and constipation are most common, caused by its irritation to the intestinal mucosa [20]. Long-term use (>6 months) may lead to elevated liver enzymes (~5% of patients) and rare but serious hypokalemia [25]. Drug-drug interactions: It inhibits CYP450 enzymes (e.g., CYP3A4, CYP2C9) and P-glycoprotein, increasing plasma concentrations of drugs like warfarin (bleeding risk), digoxin (arrhythmia risk), and statins (myopathy risk) [24]. Limited long-term data: Most RCTs last <12 months; long-term safety (e.g., potential renal toxicity) and efficacy (e.g., durability of glycemic control) remain unclear [21].

6. Conclusion

In conclusion, by introducing properties of berberine and its effect in human bodies, we have a deeper understanding to organic chemistry and the molecule (Table 1, 2). Berberine is an excellent model molecule for organic chemistry, because it demonstrates how molecular skeleton and electronic structure dictate biological activity. Its biosynthesis shows nature's elegance in building complexity, while its laboratory synthesis and modifications highlight the creativity of chemists. Mechanistically, its ability to interact with DNA, membranes, and redox systems explains its wide range of biological effects. Future research will focus on greener synthesis, selective modification, and probe development using its intrinsic fluorescence."

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