ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov940

Berberine Chloride: A Comprehensive Review of Its Pharmacology, Therapeutic Applications, and Molecular Mechanisms

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Publication Date: 2025/11/27

Abstract: Berberine chloride, an isoquinoline alkaloid derived from several medicinal plants, has gained significant scientific attention for its broad pharmacological profile. Traditionally used in Asian medicine, it is now widely investigated for its metabolic, cardiovascular, antimicrobial, and anti-inflammatory activities. This review synthesizes current evidence on the pharmacology, therapeutic potential, mechanisms of action, and safety profile of berberine chloride, with emphasis on its relevance to modern pharmacotherapy. berberine chloride demonstrates multitarget actions involving modulation of AMP-activated protein kinase (AMPK), regulation of gut microbiota, inhibition of inflammatory pathways, and improvement of glucose and lipid metabolism. Clinical studies suggest beneficial effects in conditions such as type 2 diabetes, dyslipidaemia, metabolic syndrome, and certain infectious diseases. Advances in nano formulation and delivery systems show promise for overcoming limitations in oral bioavailability. Overall, the compound exhibits a favourable safety profile, though gastrointestinal intolerance and drug–drug interactions have been reported.

Keywords: *Berberine Chloride, Pharmacotherapy, Clinical Safety, Regulation.*

How to Cite: Anita Devi; Akshit Sharma; Rajneesh Kaur; Brij Bhushan; Amandeep Kaur; Shruti Jaswal; Sarbjot Singh; Anuneet Kaur (2025). Berberine Chloride: A Comprehensive Review of Its Pharmacology, Therapeutic Applications, and Molecular Mechanisms. *International Journal of Innovative Science and Research Technology*, 10(11), 1628-1636. https://doi.org/10.38124/ijisrt/25nov940

I. INTRODUCTION

Berberine chloride is a bioactive salt form of berberine, an alkaloid compound that occurs naturally in several medicinal plants, including *Coptis chinensis* and *Berberis vulgaris*.[1] Historically, it has been used in both Chinese and Ayurvedic medicine to treat conditions such as gastrointestinal infections, like diarrhea and dysentery, and also as a natural yellow dye. Berberine chloride has a structure that includes a quaternary ammonium group, which increases its solubility in water and enhances its effectiveness in pharmaceutical use.

Recent research has uncovered a variety of health benefits associated with berberine chloride. It activates AMP-activated protein kinase (AMPK), a key enzyme involved in managing glucose and lipid metabolism [2]. This activity supports improved insulin sensitivity, reduced blood sugar levels, and increased fat breakdown, making it beneficial for individuals with type 2 diabetes, obesity, and metabolic syndrome. In addition, berberine chloride has anti-inflammatory, antioxidant, and heart-protective properties, which support its role in managing high blood pressure and atherosclerosis. In the context of cancer treatment, it can inhibit the growth of cancer cells, trigger cell death, and

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov940

prevent the formation of new blood vessels around tumours[3]. This occurs through mechanisms such as disrupting mitochondria, causing oxidative stress, and affecting pathways like NF-κB and p53.

Berberine chloride also effectively combats a wide range of microorganisms, including bacteria, fungi, and protozoa. It is especially useful against drug-resistant strains of *Escherichia coli*, which are often responsible for urinary tract infections. By reducing bacterial adhesion, biofilm formation, and virulence, it presents a possible alternative to standard antibiotics. However, its use in clinical settings is limited due to poor oral absorption and rapid metabolism in the liver, which necessitates higher doses that can lead to digestive side effects like diarrhea and stomach discomfort.

To overcome these challenges, scientists are developing advanced drug delivery systems such as liposomes, nano emulsions, and polymeric nanoparticles to improve solubility, absorption, and precision in delivering the drug. Using substances like piperine to boost bioavailability, as well as modifying the structure of berberine itself, are also being explored. Additionally, the impact of berberine on the gut microbiome is being studied, emphasizing the need for personalized treatment approaches based on an individual's microbial makeup [4].

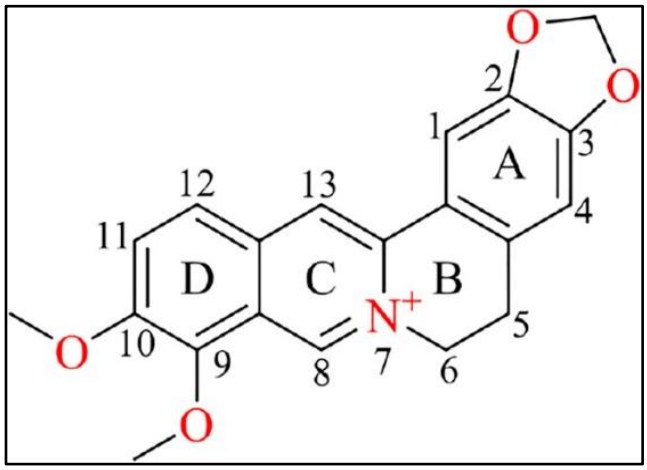

Fig 1 Structure of Bereberine

Beyond its applications in metabolic, cardiovascular, and infectious diseases, berberine chloride is under investigation for its potential in protecting the nervous system from disorders such as Alzheimer's and Parkinson's disease. These effects are linked to its antioxidant, anti-inflammatory, and ability to regulate neurotransmitters. Researchers are also working on developing new berberine analogs that offer better absorption and stronger therapeutic effects, aiming to expand its use and improve treatment outcomes [5].

In summary, berberine chloride showcases how traditional herbal medicine can contribute to modern pharmacology. Its ability to influence multiple biological pathways makes it a promising candidate for addressing complex and long-term health issues such as diabetes, cancer, infections, and neurodegenerative diseases. While challenges such as limited bioavailability persist, ongoing research into innovative delivery methods, molecular changes, and personalized treatment plans is helping to fully unlock the therapeutic potential of this ancient yet scientifically supported compound [6].

II. LITERATURE REVIEW

Berberine is a natural isoquinoline alkaloid widely recognized for its therapeutic properties, primarily extracted from medicinal plants such as *Berberis*, *Coptis*, and *Hydrastis canadensis*[7]. It exhibits significant pharmacological effects, including anti-inflammatory, antioxidant, antiapoptotic, and ant autophagic activities. These actions are mediated through the modulation of multiple key cellular pathways such as AMPK, NF-κB, SIRT1, PI3K/Akt, HIF-1α, JAK2, calcium channels, and endoplasmic reticulum (ER) stress responses. These pathways are critical in various chronic conditions, especially cardiovascular and metabolic diseases[8]. Despite its promising biological activity, berberine's clinical use remains limited due to poor oral bioavailability and limited human trials. Most existing studies are preclinical, involving cell cultures or animal models, with only a few small-scale human studies showing effects like improved lipid profiles. A 2023 review highlighted its potential to reduce cholesterol levels, though more high-quality clinical trials are needed to confirm efficacy and safety. In traditional medicine, berberine-rich plants have been used extensively across cultures. For example, *Hydrastis canadensis* and *Mahonia Aqui folium* were once used as natural remedies for gastrointestinal and skin issues in North American folk medicine. Today, over 200 species of berberine-containing plants are used globally, offering a strong foundation for drug development. However, supplement quality varies, and berberine is not FDA-approved for any specific medical use. This highlights the need for further research to standardize its use and harness its full pharmacological potential [9]. Berberine is a quaternary ammonium salt (molecular scaffold: isoquinoline alkaloid). As berberine chloride it typically appears as a yellow crystalline powder[10]. Key physicochemical characteristics include low aqueous solubility at neutral pH, better solubility in acidic media, photolability, and a relatively high melting point typical of quaternary salts. Metabolically, berberine undergoes extensive first-pass metabolism producing demethylated and oxidized metabolites (e.g., berberrubine, demethyleneberberine) which may themselves be bioactive[11]. P-glycoprotein (P-gp) mediated efflux and hepatic metabolism are major contributors to its poor systemic exposure after oral dosing. it has recently gained scientific interest due to its broad pharmacological profile, including antidiabetic, antimicrobial, anti-inflammatory, lipid-lowering, hepatoprotective, and anticancer activities[12]. Its mechanisms involve activation of AMPK, modulation of NF-κB and MAPK pathways, enhancement of insulin sensitivity, and inhibition of bacterial adhesion and biofilm formation.

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov940

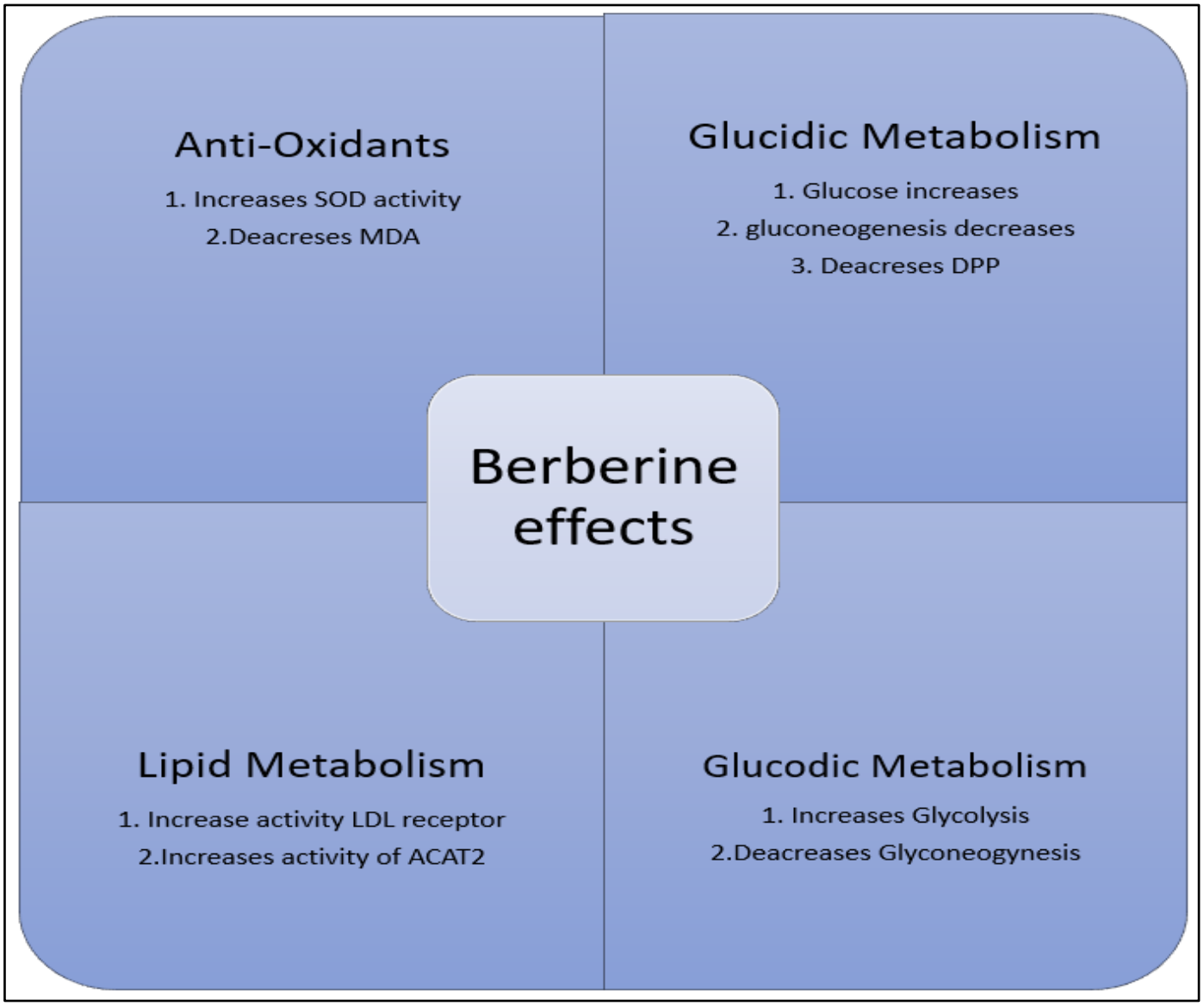

Fig 2 Berberine Effects

➢ *BBR Chemical Structure and Plant Sources:*

Berberine (BBR) is a yellow crystalline alkaloid with a molecular weight of 336.37 g/mol and a chemical formula C20H18NO4+. It is a stable compound with a bitter taste. BBR shows high solubility in polar solvents like water and ethanol but is poorly soluble in organic solvents such as acetone and ether. Among its salt forms, the hydrochloride form has lower water solubility compared to sulphate and phosphate salts, though it dissolves more easily in hot water [13].

Extraction of BBR from plants can be achieved using both traditional methods (Soxhlet extraction, percolation, maceration) and modern techniques (ultrahigh-pressure extraction, supercritical fluid extraction, microwave-assisted extraction). Ethanol and methanol are commonly employed as solvents. Extracted BBR is formulated into oral pills and capsules for clinical use. It is abundant in stems, tubers, and bark of medicinally important plants. [14]. (Table.1)

Traditionally, BBR has been widely used in Chinese medicine for centuries due to its antimicrobial, antifungal, antiprotozoal, and antiviral properties. It has also been consumed as a dietary supplement to treat conditions like the common cold, influenza, and respiratory infections [15]. (Table:1)

Table 1 BBR Chemical Structure and Plant Sources

Sr. no	Plant Sources	Plant Part	BBR content (mg/g)
1	Coptis Chinensis France	Rhizome	51-96
2	Argemone Mexicana L.	Root, Stem, Leaves	0.69-11
3	Berberis Diaphana M.	Stem, Bark	8-24
4	Berberis Croatica Horvat	Root	8-14
5	Coscinium fenestratum Colber.	Stem	11-33

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov940

III. THERAPEUTIC APPLICATIONS OF BBR

➢ *Anticancer Activity:*

BBR is one of the powerful substances utilized in anticancer therapy which is derived from a variety of plants. It is shown to have an effective activity against a wide range of cancer including breast cancer, lung cancer, cervical cancer and gastric cancer [16].

➢ *Breast Cancer:*

Breast cancer is one of the leading causes of mortality among women worldwide, and recent studies suggest that berberine (BBR) holds significant therapeutic potential against it. BBR has been shown to reduce cell viability and inhibit the multiplication of cancerous cells by targeting multiple molecular pathways. One mechanism involves lowering the levels of metatherian, a protein that promotes cancer cell growth, thereby suppressing tumour proliferation [17]. Experimental studies further demonstrate that BBR inhibits the growth of MDA-MB-468 cells by blocking cyclin D/cyclin-dependent kinase 4 (CDK4) complexes and activating the growth inhibitor p38, ultimately causing cell cycle arrest at the G1/S checkpoint [18]. Similarly, in MDA-MB-231 cells, BBR disrupts the cyclin A/CDK1 complex and suppresses the AKT/ERK signalling pathways, leading to cell cycle arrest at the G2/M phase. Beyond halting abnormal cell proliferation, BBR also induces apoptosis and reduces inflammation. Importantly, it has shown potential for synergistic effects when used in combination with conventional chemotherapy agents such as cisplatin, 5-fluorouracil, methyl methane sulfonate, and calprotectin, suggesting its promise as both a preventive and therapeutic agent in breast cancer management [19].

➢ *Lung Cancer:*

Lung cancer is one of the most aggressive and deadly malignancies worldwide, with non-small cell lung cancer (NSCLC) accounting for nearly 85% of all cases. Despite advances in chemotherapy and targeted therapy, drug resistance and poor prognosis remain major challenges. Recent studies have highlighted the anticancer potential of berberine (BBR) in NSCLC through multiple molecular pathways [20].

One of the key mechanisms by which BBR acts is the regulation of the SWI-independent-3 transcription factor, which plays an important role in cancer cell growth and survival. By interfering with this regulator, BBR effectively suppresses the growth of NSCLC xenograft tumours in experimental models. Another important mechanism is the downregulation of topoisomerase II (TOP2), a critical enzyme for DNA replication and repair. Reduced TOP2 activity leads to DNA damage, thereby triggering cancer cell death [21].

Additionally, BBR activates the miR19a/TF/MAPK signalling pathway, which promotes apoptosis and further enhances the sensitivity of lung cancer cells to cell death signals. These combined effects not only reduce tumour cell proliferation but also initiate programmed cell death, thereby limiting cancer progression [22].

Importantly, BBR has shown the ability to enhance the anticarcinogenic activity of tyrosine kinase inhibitors (TKIs), which are frontline drugs for NSCLC treatment. This suggests a potential role for BBR as an adjuvant therapy, improving drug response and overcoming resistance [23].

Overall, BBR exhibits multiple anticancer properties in lung cancer, including inhibition of cell growth, induction of apoptosis, DNA damage, and sensitization to existing therapies. However, while preclinical evidence is promising, more clinical studies are required to fully validate these mechanisms and establish BBR as a reliable therapeutic option for lung cancer patients [24].

➢ *Ovarian Cancer:*

Ovarian cancer is a major gynaecological malignancy and remains a significant health threat to women worldwide due to its high mortality rate and frequent resistance to conventional therapies. Berberine (BBR) has emerged as a promising candidate for improving the therapeutic outcomes of ovarian cancer by enhancing the effectiveness of various anticancer drugs through multiple molecular mechanisms [25].

One notable mechanism involves the caspase-dependent and RIPK3-MLKL pathways, where the combined treatment of BBR and cisplatin has been shown to inactivate ovarian cancer cells, disrupt essential cellular processes, and ultimately promote programmed cell death. This demonstrates the ability of BBR to potentiate the apoptotic and necroptotic effects of established chemotherapeutics [26].

Additionally, BBR has been found to target the iPLA2–arachidonic acid (AA)–COX-2–PGE2 pathway, which plays a role in cancer cell proliferation and inflammation. By inhibiting this pathway, BBR can reduce tumour-promoting signalling. Furthermore, in combination with the chemotherapeutic drug VP16 (etoposide), BBR was able to reverse the abnormal phosphorylation and activation of focal adhesion kinase (FAK), thereby suppressing tumour growth and enhancing drug sensitivity [27].

Another promising finding is the synergistic effect of BBR with niraparib, a PARP inhibitor commonly used in ovarian cancer treatment. Together, they induce significant DNA damage in cancer cells, thereby blocking their survival and proliferation.

Overall, these findings indicate that BBR has strong potential to act as an adjuvant therapy in ovarian cancer by enhancing the efficacy of existing anticancer drugs through diverse molecular pathways, including apoptosis, necroptosis, inhibition of inflammatory signalling, and DNA damage induction. However, further mechanistic and clinical studies are required to validate these results and to translate BBR-based therapies into effective clinical strategies for ovarian cancer management [28].

➢ *Gastric Cancer:*

Stomach cancer, also known as gastric cancer, is one of the most common and deadly malignancies worldwide. Recent studies have demonstrated that berberine (BBR)

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possesses strong preventive and therapeutic potential against this disease through multiple molecular mechanisms [29]. One important pathway involves the inhibition of SGC-7901 gastric cancer cell proliferation by blocking the cell cycle at the G1 phase, thereby preventing uncontrolled cell division. Both in vitro and in vivo experiments have further confirmed that BBR suppresses tumour growth and significantly reduces the secretion of interleukin-8 (IL-8), a pro-inflammatory cytokine that supports cancer progression, through the inactivation of MAPK signalling pathways [30].

Additionally, BBR has been shown to interfere with two key oncogenic regulators: the STAT3 signalling pathway and the epidermal growth factor receptor (EGFR). By suppressing STAT3 stimulation and inhibiting EGFR phosphorylation, BBR disrupts critical signals required for gastric cancer cell survival, proliferation, and metastasis. Together, these mechanisms highlight the multifaceted role of BBR in reducing inflammation, blocking proliferative signalling, and inducing cell cycle arrest, making it a promising candidate for stomach cancer prevention and therapy [31].

➢ *Effect Against Diabetes:*

Berberine (BBR) has been shown to play a significant role in regulating lipid and carbohydrate metabolism, particularly in maintaining glucose homeostasis. Recent preclinical and clinical studies have highlighted its potential as an antidiabetic agent. Mechanistically, BBR stimulates insulin receptor activity in the liver and skeletal muscle by promoting protein kinase C–dependent pathways [32]. Yin and colleagues provided strong evidence for its therapeutic use in type 2 diabetes by demonstrating a substantial reduction in both fasting and postprandial blood glucose levels throughout their study. Their results revealed that fasting plasma insulin levels decreased by 28.1%, while the homeostasis model assessment index for insulin resistance fell by 44.7% ($p < 0.001$). Moreover, glycated haemoglobin (HbA1C) levels were significantly reduced from 8.1 ± 0.2 to $7.3 \pm 0.3\%$ ($p < 0.001$), indicating long-term glycaemic control [33].

In addition to its hypoglycaemic activity, the clinical trial findings suggested that BBR exerts beneficial effects on lipid metabolism, making it a promising candidate for metabolic syndrome management. Although 20 participants (34.5%) reported temporary gastrointestinal disturbances, no cases of liver or renal toxicity were observed, supporting its overall safety profile [34]. These outcomes highlight the therapeutic value of BBR as a natural compound capable of improving both glucose and lipid parameters, especially in individuals with type 2 diabetes. Its dual mechanism—enhancing insulin sensitivity while lowering lipid levels—sets it apart from many conventional oral hypoglycaemic agents[35].

Further insights into the cellular mechanisms were provided by Kong and colleagues, who investigated how BBR improves insulin sensitivity. Their study revealed that BBR activates the insulin receptor (InsR) in a dose- and time-dependent manner, leading to increased InsR mRNA and protein expression in human liver cells. When tested in diabetic mice with insulin-deficient type 2 diabetes, BBR significantly reduced blood glucose levels, although it did not show effectiveness in autoimmune type 1 diabetes (NOD/LtJ model). These findings suggest that BBR is a unique phytochemical with targeted action against insulin resistance, reinforcing its therapeutic potential for type 2 diabetes mellitus, but not type 1[36].

IV. PHARMACOLOGY OF BERBERINE

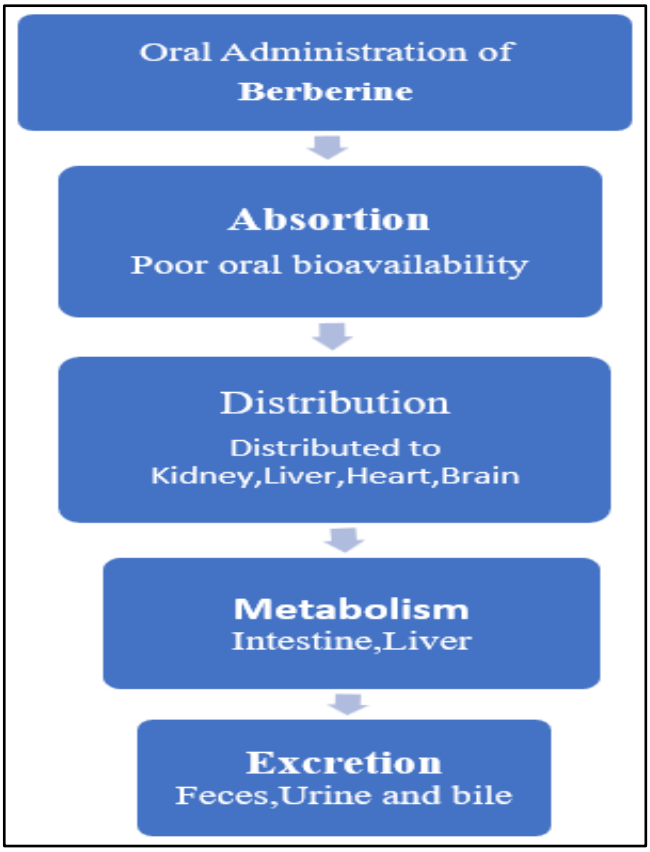

Fig 3 Pharmacology of Berberine

➢ *Absorption:*

Berberine has extremely low oral bioavailability, mainly due to P-glycoprotein (P-gp)–mediated efflux in the intestine and liver, where P-gp actively expels nearly 90% of absorbed berberine back into the intestinal lumen, greatly limiting its systemic availability (Chae et al., 2008). However, studies have shown that co-administration with P-gp inhibitors such as cyclosporine A and verapamil can significantly enhance its intestinal absorption by blocking this efflux mechanism (Pan et al., 2002), suggesting that modulation of transporter activity or the use of advanced drug delivery systems may help overcome this barrier and improve berberine's therapeutic effectiveness [37].

➢ *Distribution:*

Animal studies have demonstrated that, following oral administration, berberine exhibits a wide tissue distribution, with rapid accumulation in the liver, kidney, heart, brain, lungs, muscle, pancreas, and adipose tissue (Tan et al., 2013). This broad distribution pattern suggests its potential to act on multiple organs and systems; however, despite these

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov940

promising preclinical findings, there are currently no human studies available that clearly describe the distribution of berberine in human tissues (Ime Shahidi et al., 2019)[38].

➢ *Metabolism:*

Berberine undergoes extensive hepatic metabolism in both humans and animals. In the phase I metabolic stage, it primarily experiences demethylation, followed by phase II reactions where the resulting compounds are conjugated with glucuronic acid or sulfuric acid to produce more polar, excretable metabolites (Qiu et al., 2008)[39]. After oral administration of berberine chloride (0.9 g/day for three days) in healthy males, three main sulphate metabolites were identified in urine: jatrorrhizine-3-sulfate, thalifendine-10-sulfate, and the major metabolite demethyleneberberine-2-sulfate. Additional studies identified six novel glucuronide and sulphate conjugates in urine samples from both rats and humans, such as berberrubine-9-O-glucuronide, thalifendine-10-O-glucuronide, and demethyleneberberine-2,3-di-O-glucuronide, highlighting the complex metabolic profile of berberine. An in-depth pharmacokinetic study in male Sprague-Dawley rats further revealed that both phase I and phase II metabolites are excreted in bile, urine, and faces, including multiple hydroxylated and demethylated derivatives, such as thalifendine, berberrubine, jatrorrhizine, and palmitin, along with their glucuronide and sulphate conjugates (Ma et al., 2013b). Interestingly, preclinical studies suggest that these metabolites may be the actual pharmacologically active forms of berberine in vivo, especially following oral administration (Cao et al., 2013; Zhou et al., 2014). This complex metabolic transformation explains berberine's systemic effects despite its low parent drug bioavailability [40].

➢ *Excretion:*

Following oral administration of berberine at a dose of 200 mg/kg in rats, the compound and its metabolites were primarily excreted through bile, urine, and fences, with a total recovery rate of 22.83%—including 19.07% as unchanged (prototype) berberine and 3.76% as its metabolites (Ma et al., 2013b). The excretion was found to be most significant via the focal route, which accounted for 22.74% of the dose within 48 hours, indicating poor absorption and high gastrointestinal clearance. A smaller portion was recovered from bile (9.2%) and urine (0.0939%) over similar time frames [41]. The major portion (84%) of berberine and its metabolites was excreted via feces, suggesting limited systemic exposure and significant biliary elimination. In bile, around 83% of excreted berberine appeared mainly in the form of thalifendine, while urinary excretion was dominated by thalifendine and berberrubine, which together accounted for 78% of berberine-derived compounds in urine. These findings reflect berberine's extensive hepatic metabolism, enterohepatic circulation, and primary gastrointestinal excretion pathway, contributing to its low oral bioavailability despite widespread tissue distribution [42].

➢ *Pharmacological Activity of Berberine Chloride Drug:*

Berberine (BBR) is a bioactive natural compound with a long-standing history of medicinal use, particularly in traditional Chinese medicine (TCM). With over 3000 years of therapeutic application across Asia, berberine has been traditionally used to treat conditions related to heat, blood toxicity, and dampness. It is primarily found in plants belonging to the Burseraceae, Papaveraceae, and Ranunculaceae families. Key herbal sources such as *Coptis chinensis* (Weilian), *Coptis deltoidea* (Yalian), and *Coptidis rhizome* (Huanglian) are particularly rich in berberine and have been mentioned in several ancient Chinese medical texts, including the *Shen Nong's Herbal Classic* (200 A.D.), *Shang Han Lun*, *Jin Kui Yao Lue* (210 A.D.), *Wai Tai Mi Yao* (752 A.D.), and *Ben Cao Gang* (1596 A.D.) [43].

Berberine is also a central component in numerous traditional Chinese polyherbal formulations, known as "Fu fang." Out of the 1760 traditional formulae recorded in Chinese medical literature, over 100 include berberine-rich components, such as the well-known decoctions *Xie Xin* and *Huanglian Jiedu*. These formulations continue to be used in modern Chinese medicine, including in anti-inflammatory and antipyretic preparations like *San-Huang-Xie-Xin-Tang* and "San Huang" tablets. Beyond traditional use, scientific evidence has increasingly validated berberine's therapeutic benefits, demonstrating efficacy against inflammation, microbial infections, diabetes, cancer, and neurodegenerative diseases [44].

Pharmacologically, berberine displays a broad range of biological activities, including antioxidant, anti-inflammatory, anti-apoptotic, anti-diabetic, lipid-lowering, and anticancer effects. These multifaceted actions have not only solidified its role in traditional Asian medicine but have also led to its acceptance as a dietary supplement in parts of Europe and Africa, where it is used to alleviate fever, respiratory infections, and flu-like symptoms. Ongoing research continues to explore its protective effects on various organs, reinforcing berberine's value as a promising natural therapeutic agent [45].

It can inhibit the production of inflammatory cytokines, reduce the activity of inflammatory pathways like NF-κB and MAPK, and alleviate symptoms of inflammatory conditions. Berberine has been studied for its potential in treating various inflammatory conditions, including mastitis, intestinal inflammation, and diabetes-related [46].

V. DISCUSSION

The physicochemical profiling of berberine chloride, particularly involving molecular descriptors such as percent human serum albumin binding (%HSA), topological polar surface area (tPSA), log P, solubility, and pKa, plays a crucial role in predicting its oral absorption and formulation behaviour. Parameters like tPSA are directly related to the hydrophilicity and membrane transport characteristics of drug molecules [47]. The compound's apparent log P values, both computational and experimental, confirm its hydrophilic nature, although variations occur due to different calculation methods. Despite being permanently charged and non-ionizable, berberine chloride shows unusual pH-dependent solubility behaviour—its solubility significantly increases in phosphate buffer at pH 7.0, likely due to drug–buffer salt

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov940

interactions that form more soluble complexes. Temperature also influences solubility, with a 62% increase observed between 25°C and 37°C, suggesting endothermic solubilization dynamics [48].

Attempts to enhance its solubility using surfactants yielded mixed results. Non-ionic surfactants had no effect, while ionic surfactants like SLS and CTAB reduced solubility—SLS caused the formation of insoluble salts, and CTAB likely induced electrostatic repulsion. As a result, cyclodextrin (CD) complexation was explored as a solubility enhancement strategy. Among the tested β-CD derivatives, hydroxypropyl-β-cyclodextrin (HPβCD) demonstrated superior performance compared to randomly methylated-β-cyclodextrin (RMβCD), showing higher stability constant (Ks), complexation efficiency (CE), and solubility improvement. A 25% HPβCD concentration was found sufficient to solubilize a 10 mg/mL dose of berberine chloride [49].

Further characterization using techniques like differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), and scanning electron microscopy (SEM) confirmed the formation of a 1:1 inclusion complex. DSC results revealed the disappearance of the drug's melting peak, indicating loss of crystallinity [50]. FTIR showed the absence of specific functional group peaks, implying successful encapsulation, while NMR shifts supported the insertion of berberine's structural rings into the CD cavity. SEM images also confirmed morphological changes consistent with complexation [51]. Altogether, these findings highlight cyclodextrin complexation—particularly with HPβCD—as a promising and effective approach for enhancing the aqueous solubility and formulation stability of berberine chloride for oral dosage forms [52].

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