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Exploring Transdermal Drug Delivery Systems for Berberine: A Versatile Phytoconstituent for Multi-Disease Management

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ABSTRACT:

Berberine is a quaternary benzyloquinoline alkaloid with multiple pharmacological effects used for the treatment of hypertension, tumors, bacterial infections, inflammation, HIV, and cardiac diseases. In phase I clinical trials, Berberine is safe at excessive doses but manifests poor bioavailability. Major challenges like poor absorption, rapid metabolism, and rapid systemic Elimination are responsible for low plasma and tissue levels of berberine. Various strategies have been undertaken by several Researchers to overcome this issue and enhance the bioavailability of berberine. This includes the design of new formulation Strategies; novel drug delivery systems (NDDS) like liposomes, nanosized dosage forms, phospholipid complexes, muco-Adhesive microparticles, and micoemulsions; the use of adjuvants; and the design of structural analogous of berberine. This Review focuses on the occurrence of berberine in numerous plants and its pharmacological activities as evidenced through Numerous preclinical and clinical studies. The later part of this review highlights the bioavailability issue of berberine which Arises due to its poor absorption, elevated rate and extent of metabolism, and quick elimination and clearance from the body. A systematic effort has been made to analyze the various formulation strategies, including the design of newer berberine Analogues and derivatives. These strategies can be further explored to increase the bioavailability, medicinal value, and application of this promising molecule.



INTRODUCTION

Berberine(5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a] quino-lizinium) is an isoquinoline alkaloid with a Molar mass of 336.3612 g/mol. It is present as a non-basic and quaternary protoberberine in several herbs, including European barberry, goldenseal, goldthread, Oregon grape, philodendron, and tree turmeric. The reported uses of berberine Containing species are summarized in Table 1. Berberine (BBR) is a yellowish crystalline powder with a faint characteristic odour and Sour taste. It is moderately soluble in methanol, with marginally solubility in ethanol and water. Berberine is reactive to light and heat; when exposed to high temperature and light, it undergoes degradation and thus affects its stability. Several pharmacological effects of BBR are reported in literature, which includes anti-depressant (Sun et al., 2014), Anti-atherosclerosis (Sarna, Wu, Hwang, Siow, & O, 2010), anti-diarrheal (Zhang et al., 2012b), anti-osteoporosis (Lee et al., 2008), anti-Hypercholesterolemia (Kong et al., 2008), and neuroprotective effects (Zhang et al., 2012a). Reports on the extraction of different BBR-employing techniques (classical and conventional methods) using different solvents like methanol, ethanol, and aqueous or Acidified methanol/ethanol are available in literature. Conventional methods enhance the extraction efficiency and reduce extraction times and solvent volumes used in the extraction process when compared to the classical methods. BBR in plant extracts and In biological fluids have been quantified using analytical techniques like Ultra Violet spectroscopy (UV), High Performance Liquid Chromatography (HPLC), High Performance Thin Layer Chromatography (HPTLC), Thin Layer Chromatography (TLC), Capillary Electrophoresis (CE), and Liquid Chromatography coupled with

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Mass Spectrometry (LC-MS).BBR is present in several plants and is also reported to be re-

sponsible for numerous biological activities. Table 1 summarizes the plant species, content of berberine in plant parts, and their reported biological activities. BBR is also present in several marketed herbal preparations, either in pure chemical form as berberine or as plant extracts. However the major drawback of BBR is its low bioavailability and poor pharmacokinetics, which is majorly responsible for its reduced efficacy. The foremost objective of this review is to discuss in detail the bioavailability, factors controlling bioavailability, and means to improve the bioavailability of BBR.

Causes

1. Extensive First-Pass Metabolism
2. Poor Solubility & Ionization Effect
3. Widespread P-gp Efflux
4. Rapid Clearance and Short Half-Life
5. GI Side Effects
6. Variable Microbiome Metabolise

Rationale for using transdermal route

1. A transdermal formulation comprising,
 - (a) An aqueous phase comprising water and at least one water soluble emulsion stabilizer;
 - (b) An oil phase comprising at least one emulsifier, at least one oil soluble emulsion stabilizer, at least one emollient comprising at least one flavonoid and at least one other emollient;Wherein the oil and aqueous phase form an emulsion;an external phase comprising at least one flavonoid containing-extract, at least one phospholipid-complexed flavonoid and at least one source of berberine
 - (c) At least one preservative phase.

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2. The transdermal formulation of claim 1, further comprising antioxidants and/or reducing agents.
3. The transdermal formulation of claim 2, wherein the antioxidants are selected from one or more of vitamins, extracted polyphenols and non-essential amino acids.
4. The transdermal formulation of any one of claims 1 to 3, wherein the source of berberine or analog thereof is selected from one or more of barberry extract, meadow rue, celandine, *Berberis aquifolium*, *Berberis vulgaris*, *Hydrastis Canadensis*, *Xanthorhiza simplicissima*, *Phellodendron amurense californica* and *Mahonia aquifolium*.
5. The transdermal formulation of claim 4, wherein the source of berberine is an extract from *Berberis vulgaris*.
6. The transdermal formulation of claim 4, wherein the source of berberine is an extract from *Hydrastis Canadensis*.
7. The transdermal formulation of claim 4, wherein the source of berberine is an extract from *Mahonia aquifolium*.
8. The transdermal formulation of any one of claims 1 to 8, wherein the source of berberine or analog thereof is present in the formulation in an amount of about 1% wt% to about 20 wt%, or about 3 wt% to about 15 wt%, of the total formulation.
9. The transdermal formulation of any one of claims 1 to 8, wherein the berberine analog or derivative is selected from one or more of berberine, berberine sulfate, berberine bisulfate, berberine hemisulfate, berberine chloride, jatrorrhizine, palmatine, coptisine, 8-ethyl-12-bromoberberine, 8-ethylberberine, 8-methoxyberberine, 8-methylberberine, 8-n-butyl-12-bromoberberine, 8-n-butylberberine, 8-n-hexyl-12-bromoberberine, 8-n-propyl-12-bromoberberine, 8-n-propylberberine,
10. The transdermal formulation of claim 9, wherein the berberine analog is dihydroberberine or tetrahydroberberine.
11. The transdermal formulation of any one of claims 1 to 10, further comprising one or more statins.
12. The transdermal formulation of claim 11, wherein the one or more statins are selected from atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.
13. The transdermal formulation of any one of claims 1 to 12 in the form of a cream, gel, liquid suspension, ointment, solution or patch.
14. The transdermal formulation of any one of claims 1 to 12, in the form of a cream.
15. The transdermal formulation of claim 14, wherein the cream has a viscosity of about 50000 cps to about 500000 cps, or about 85000 cps to about 200000 cps as measured using a Brookfield RVT T4 2 RPM instrument at room temperature.

Pharmacological Effects of Berberine Oxidative Stress

The effect of berberine on a variety of neurodegenerative diseases indicates that it may have a regulatory effect on the common pathways of these diseases. MAO-B inhibitors are believed to have a positive effect on patients with Alzheimer's and Parkinson's disease. The dopamine metabolic pathway mediated by MAO-B can generate



hydrogen peroxide (H₂O₂), and with the increase of MAO-B activity, excessive H₂O₂ leads to oxidative stress and neuronal damage (Jiang et al., 2015a). Therefore, the antioxidant effect of berberine has great effects on the treatment of neurodegenerative diseases.

The pathogenesis of neurodegenerative diseases has several common features, such as oxidative damage and mitochondrial dysfunction. Among them, oxidative stress refers to the excessive accumulation of reactive oxygen species (ROS) that leads to the imbalance of oxidants and antioxidants, oxidative stress has the ability to lead to mitochondrial dysfunction and lysosome dysfunction, and ultimately induces neurodegenerative diseases. It has been reported that Berberine significantly reduces ROS production in the cytoplasm and mitochondria (Sun et al., 2017). This effect may be related to the activation of AMP-activated protein kinase (AMPK) and sirtuin1 (SIRT1)/forkhead box O1 (FOXO1) pathway. In addition, in PC12 and N2a cells, low-concentration administration of berberine significantly reduced the amount of ROS generation, lipid peroxidation, and DNA fragmentation, and at the same time increased glutathione content and superoxide dismutase activity (Sadeghnia et al., 2017). As we all know, the body has both enzymatic (such as glutathione-S-transferase) and non-enzymatic (such as thiols and reduced glutathione) antioxidant mechanisms to combat oxidative damage. Once ROS overwhelms the antioxidant activity of the cell, oxidative stress occurs (Lee et al., 2012; de Oliveira et al., 2019). Berberine-induced increase in heme oxygenase-1 (HO-1, an antioxidant enzyme) mRNA and protein expression is positively correlated with concentration and continuous administration time. This effect can be antago-

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nized by kinase-protein kinase B (AKT) inhibitors and phosphatidylinositol 3-kinase (PI3K) inhibitors (Chen et al., 2012). An in-vitro study found that berberine protected NSC34 cells from H₂O₂-induced cytotoxicity by reducing ROS production, restoring glutathione, and superoxide dismutase activity, and activating the production of antioxidant proteins nuclear factor erythroid 2-related factor-2 (Nrf2) and HO-1 (Hsu et al., 2012; Fan D. et al., 2019a).

Studies have found that berberine has an antidepressant effect (Kulkarni and Dhir, 2008; Fan et al., 2017), acute administration can increase dopamine, serotonin and norepinephrine levels in the whole brains of mice, and this effect can be antagonized by l-arginine or sildenafil pretreatment. In short, berberine can play an antidepressant effect by regulating brain biogenic amines and nitric oxide pathway (Kulkarni and Dhir, 2008). Besides, the treatment of berberine can reduce the activity of ecto-nucleoside triphosphate diphosphohydrolase (NTPDases) and 5'-nucleotidase in the cerebral cortex and hippocampus (de Oliveira et al., 2019). In brief, the application of berberine provides a promising neuroprotective therapy for neurodegenerative diseases induced by oxidative damage, such as Alzheimer's disease, Parkinson's disease (Figure 1). It may be playing an antioxidant role by reducing ROS, iNOS, COX-2, increasing HO-1, and activating SIRT/FOXO1 signal pathway. Berberine can also play a therapeutic role by increasing glutathione and superoxide dismutase activity. In addition, whether the antioxidant effect of berberine alters other markers needs to be further explored.

The pharmacological effects of berberine. This schematic drawing shows the anti-oxidant, anti-inflammatory and neuroprotective



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tive effects of berberine and its related molecular mechanisms. ROS, reactive oxygen species; COX-2, cyclooxygenase-2; iNOS, nitric oxide synthase; HO-1, heme oxygenase-1; SIRT1, sirtuin1; FOXO1, forkhead box O1; IL-1 β , interleukin 1 β ; IL-6, interleukin 6; TNF- α , tumor necrosis factor- α ; GFAP, glial fibrillary acidic protein; SphK1, sphingosine kinase-1; S1P, sphingosine-1-phosphate; p-CREB, phosphorylated cAMP response element binding protein; NF- κ B, nuclear transcription factor kappa B; A β , amyloid β ; APP, amyloid precursor protein; BACE1, beta-secretase 1; PI3K, phosphatidylinositol 3-kinase; AKT, kinase-protein kinase B; Nrf2, nuclear factor erythroid 2-related factor-2; JNK, jun amino-terminal kinases.

Neuroprotection

In vitro experimental results show that berberine can reduce 6-hydroxydopamine-induced reactive oxygen generation and caspase-3 activation in SH-SY5Y cell. In addition, berberine can induce activation of PI3K/AKT signaling pathway, which is related to Nrf2 expression and neuroprotection (Bae et al., 2013). Similarly, it has been confirmed in PC-12 cells that berberine exerts a neuroprotective effect by activating the PI3K/AKT signaling pathway and Nrf2/HO-1 antioxidant signaling pathway (Zhang et al., 2017). In BV2 and N2a cells treated with amyloid β (A β), berberine promotes cell proliferation, inhibits the activity of caspase-3, and reduces the rate of apoptosis, in addition, berberine promotes cell viability via the microRNA (miR)-188/nitric oxide synthase 1 (NOS1) pathway (Chen M. et al., 2020a). By analyzing the

learning and memory of post-cerebral ischaemia. Animals, the researchers discovered the neuroprotective effects of berberine (Ye et al., 2009; Zhang C. C. et al.,

2018a). In vitro experiments (organotypic hippocampal culture exposed to oxygen and glucose deprivation), the culture treated with berberine has less cellular death. In further research, it was found that the neuroprotection mediated by berberine after ischemia involves the AKT/glycogen synthase kinase-3 β (GSK3 β)/extracellular signal-regulated kinase 1/2 (ERK 1/2) signal pathway, and inhibits Jun amino-terminal kinases (JNK) and caspase-3 activity (Simões Pires et al., 2014).

Berberine inhibits neuronal apoptosis by regulating autophagy-related proteins [Microtubule-associated protein 1A/1B-light chain 3 (LC3), Beclin-1, p62], and apoptosis regulatory proteins [caspase 3, caspase 8, caspase 9, poly ADP-ribose polymerase (PARP), and B-cell lymphoma 2 (Bcl-2)/Bcl-2 associated X (Bax)] (Zhang et al., 2016). Similarly, berberine shows anti-apoptotic effects by reducing the overexpression of caspase-3 and Bax/Bcl-2 (Sadeghnia et al., 2017). In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine/probenecid (MPTP/P)-induced Parkinson's disease model mice, MPTP/P injection increased the ratio of Bax/Bcl-2 and the expression of caspase-3 in the hippocampus, while berberine administration reversed these effects (Kim et al., 2014).

In addition, animal experiments and cell experiments have confirmed that berberine reduces the levels of extracellular and intracellular A β , increases the levels of LC3-II, Beclin-1, hVps34 and cathepsin-D, and reduced the levels of P62, Bcl-2, amyloid precursor protein (APP), and beta-secretase 1 (BACE1). Briefly, berberine plays a neuroprotective effect by promoting autophagy clearance and reducing A β production

Besides, it is indicating that berberine facilitates nerve regeneration via JNK-AKT signal pathway mediated by insulin-like growth factor receptor (Zhang H. N. et al.,



2018b). In astrocytes, berberine reduces glutamate-induced cytotoxicity by reducing mitochondrial fragmentation and neurodegeneration. Additionally, berberine prolongs the incubation period of epileptic seizures in a dose-dependent manner. Long-term administration of berberine reduces the level of malondialdehyde in epileptic mice and enhances the activities of glutathione and catalase (Gao et al., 2014). In addition, the neuroprotective role of berberine is related to the decrease in endoplasmic reticulum stress and oxidative stress. Berberine can also be used in combination with other drugs such as levetiracetam and curcumin to enhance its neuroprotective effect by reducing inflammation and oxidative stress. In vitro, low-dose berberine significantly increased PC12 cell viability, whereas high-dose berberine did the opposite (Zhang et al., 2017). Additionally, low-dose berberine protected PC12 cells from 6-hydroxydopamine (6-OHDA, Parkinson's disease-related neurotoxin)-induced cytotoxicity and apoptosis, whereas high-dose berberine showed no neuroprotective activity. Further experiments found that low-dose berberine can promote cell survival and antioxidant effects by up-regulating PI3K/AKT/Bcl-2 and Nrf2/HO-1 signal pathways. In animal studies, low-dose berberine attenuated 6-OHDA-induced loss of dopaminergic neurons and hypokinesia in zebrafish, whereas high-dose berberine had no apparent effect. These suggest that the neuroprotective effects of berberine may be related to an excitatory mechanism that promotes cell survival and antioxidant-related signaling pathways. Studies have found that berberine attenuates ischemia-reperfusion injury through NF- κ B nuclear translocation in mice with transient cerebral artery occlusion, however, this neuroprotective effect was more pronounced at the high dose (50 mg/kg) than the low dose (25 mg/kg)

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(Zhu et al., 2018). These differences may be related to different concentrations of berberine and different models of nerve injury.

Neuroinflammation

Some studies have shown that berberine activates macrophages and increases their phagocytic function, increases the production of interleukin (IL)-1, and enhances non-specific immunity, can be used as a neuroprotective agent to prevent Alzheimer's disease. Long-term administration of berberine increases the expression of IL-1 β and inducible nitric oxide synthase (iNOS) in Alzheimer's disease mice hippocampus, and ameliorate memory impairment (Zhu and Qian, 2006). Besides, berberine down-regulates the expression of acetylcholinesterase and inhibits acetylcholinesterase activity in Alzheimer's disease model mice hippocampus which induced by heavy metals, in addition, berberine normalizes the production of inflammatory factors, such as tumor necrosis factor- α (TNF- α), IL-6, IL-1 β (Hussien et al., 2018). Studies demonstrated that berberine contributed to AMPK signaling pathway activation and participate in anti-neuroinflammation. In BV-2 microglia, berberine down-regulates lipopolysaccharide- or interferon- γ -induced iNOS and cyclooxygenase-2 (COX-2) level, and inhibits inflammatory cytokines expression (for example IL-6, IL-1 β , TNF- α) (Lu et al., 2010). On the other hand, berberine can inhibit ERK phosphorylation (Lu et al., 2010), and induce the phosphorylation of Liver kinase B1 (LKB1) (Ser428), calcium/calmodulin-dependent protein kinase II (CaMKII) (Thr286), and AMPK (Thr172) (Lu et al., 2010). In animal experiments, berberine has the ability to improve learning and memory impairment in rats via lipopolysaccharide. Further studies showed that berberine en-



hanced the activities of glutathione peroxidase, glutathione, superoxide dismutase, and catalase, further reducing the activity of acetylcholinesterase and caspase-3, protein carbonyl, and DNA fragmentation in the hippocampus. In addition, berberine can properly restore the levels of 3-nitrotyrosine (3-NT), COX 2, glial fibrillary acidic protein (GFAP), and sirtuin 1 in the hippocampus (Sadraie et al., 2019). Besides, the protective effect of berberine resisting MTPT-induced toxicity may be related to the enhancement of autophagy by berberine through AMPK-dependent pathways (Deng and Ma, 2021).

The study found that berberine alleviated the severity of symptoms in the multiple sclerosis mouse model, and in primary astrocyte culture, berberine inhibited the increase in sphingosine kinase-1 (SphK1), and Sphingosine-1-phosphate (S1P) induced by lipopolysaccharide. A number of researchers have reported that the activation of the SphK1/S1P signaling pathway marks the occurrence of autoimmune diseases, and the up-regulation of SphK1 is related to the pathogenesis of multiple sclerosis. In Alzheimer's disease mice, GFAP and neuron loss increased and neuronal nuclei (NeuN) decreased significantly. Studies have found that under pathological conditions, astrocytes are activated by A β to produce cytoinflammatory factors, complement, oxygen free radicals, etc., which then trigger inflammation, promote nerve cell damage and death, and ultimately aggravate Alzheimer's disease. The latest research shows that berberine significantly decreases the expression of GFAP in the Alzheimer's disease mice hippocampus, indicating berberine inhibits the overexpression of astrocytes in Alzheimer's disease mice. These may be linked to the effect of berberine on improving local blood flow, reducing the production of A β and reducing cell

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apoptosis. Similarly, berberine treatment can significantly reduce the oxidative stress in diabetic rat hippocampus and suppress GFAP immunoreactive astrocytes (Moghaddam et al., 2014). Astrocytes treated with berberine can increase the expression of p85 and p-AKT. Berberine also increases the accumulation of Nrf2 and DNA binding activity in the nucleus. It is worth noting that the increase in Nrf2 DNA binding activity induced by berberine can be antagonized by PI3K inhibitors and AKT inhibitors. In other words, in astrocytes. The increase in HO-1 expression induced by berberine is activated by Nrf2 activation through PI3K/AKT signaling pathway. Similarly, in SH-SY5Y cells, berberine resists rotenone-induced neurotoxicity through antioxidant effects and activates the PI3K/AKT signaling pathway.

Therapeutic Effects of Berberine on Neurodegenerative Disease

In recent years, many studies surrounded the effect of berberine in central nervous system disease, including Alzheimer's disease, Parkinson's disease, Huntington disease, etc. (Jiang et al., 2011; Kim et al., 2014; Jiang et al., 2015b; Bandiwadkar et al., 2021). Berberine has proven its protective role on oxidative stress, neuroinflammation, neuroprotection, etc. (Zhang et al., 2012; Maleki et al., 2018; de Oliveira et al., 2019; Li Z. et al., 2020a; Qin et al., 2020; Rezaeian et al., 2020; Mohi-Ud-Din et al., 2021). And whether it can be used to improve the symptoms of neurodegenerative diseases has attracted widespread attention.

Alzheimer's Disease

Alzheimer's disease, an age-related neurodegenerative disease, affects the quality of life of patients, and their families. Patient with Alzheimer's disease suffer from



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memory loss, cognitive decline, energy metabolism dysregulation, changes in personality, and behavior (Goedert and Spillantini, 2006; Ribeiro et al., 2017; Shinjyo and Kita, 2021). Although a considerable new research progress has been made in Alzheimer's disease research, the pathogenesis remains unclear. Current typical histopathological changes in Alzheimer's disease include A β plaques and tau tangles, the accumulation of these proteins leads to neuroinflammation and normal dysfunction, leading to neuronal death (Ameen and Michniak-Kohn, 2017; Bandiwadkar et al., 2021; Ye et al., 2021). The hypotheses on the pathogenesis of Alzheimer's disease include cholinergic hypothesis, amyloid toxicity hypothesis, oxidative stress hypothesis, etc. (Ye et al., 2009; Guo et al., 2021). At present, the therapies of Alzheimer's disease include stem cell therapy, gene therapy, and chemotherapy, but these therapies have limitations inevitably such as inefficient and neurotoxicity (Bandiwadkar et al., 2021). At the same time, natural compounds have better compatibility with the human body and have fewer side effects. A number of studies have shown that some natural drugs have significant neuroprotective, anti-oxidant and anti-inflammatory characteristics, and are suitable for the treatment of different types of neurodegenerative diseases (Ahmed et al., 2015; Jiang et al., 2015b; Fan et al., 2017; Zhang et al., 2020). Many literatures have reported the improvement effect of berberine on Alzheimer's disease (Chen M. et al., 2020a; Chen Y. et al., 2020b; Xuan et al., 2020; Raju et al., 2021).

A β has a neurotoxic effect, which can lead to neuronal degeneration, death, apoptosis, and decrease in the number of synapses and ultimately lead to cognitive impairment and behavioral abnormalities (Li W. et al., 2020b; Ye et al., 2021). It has proved that

activating microglia by reducing A β is an effective treatment for Alzheimer's disease. Microglia exerts a vital role on the repair of central nervous system damage. In Alzheimer's disease, the production of pro-inflammatory factors and A β can over-activate microglia, secrete inflammatory factors and neurotoxins, and then induce neuronal damage and even apoptosis, thereby triggering Alzheimer's disease. On the contrary, microglia can also protect the central nervous system by engulfing A β , slowing the development of Alzheimer's disease (Li et al., 2021). Study have shown berberine can inhibit A β -induced microglial activation mediated by suppressor of cytokine signaling 1 (SOCS1) (Guo et al., 2021). Berberine induces the production of antioxidant A β 40 and inhibits the formation of A β 42, which is the cause of A β plaque accumulation, and then exerts a neuroprotective effect (Hussien et al., 2018). Besides, berberine inhibits the p-ERK/Eukaryotic translation initiation factor 2 α (eIF2 α) pathway and then reduces BACE1 expression, the decrease in BACE1 protein expression inhibits the production of A β . In other words, berberine suppressed A β production via inhibiting protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK)/eukaryotic translation-init

Cardiovascular diseases (including atherosclerosis, myocardial infarction, hypertension, cardiac hypertrophy and heart failure), and metabolic diseases (including diabetes, obesity, and non-alcoholic fatty liver disease), are the leading causes of death worldwide 1-8. These diseases are caused by the combined effects of multiple pathological factors, and their pathogenesis has not been fully clarified yet 1-8. Although the prevention and treatment of cardiovascular diseases and metabolic diseases (CVMD) have made great progress in the past 20 years, the



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morbidity and mortality arising from CVMD are still very high 1-8. Western medicine is still the mainstream therapy of CVMD 9-12. For example, hypoglycemic agents, statins, anticoagulants, beta receptor blockers, nitrates, and anti-thrombotic drugs are widely used in patients with CVMD 9-11, 13, 14. Despite widespread evidences showing that these drugs are effective in a treatment of CVMD, potentially serious adverse consequences remain key challenges 9-14. Therefore, there is an urgent need to identify alternative and complementary therapies to better manage CVMD.

Therapeutic potential of BBR in cardiometabolic diseases. Current researches support that BBR may play a therapeutic role in the treatment of cardiovascular disease (including atherosclerosis, heart failure myocardial infarction, arrhythmia, abdominal aortic aneurysm, stroke) and metabolic diseases (including nonalcoholic fatty liver, obesity, diabetes and its cardiovascular complications).

1. Low Solubility

Description: Berberine is poorly soluble in water, especially at physiological pH (~7.4), which limits its dissolution in the gastrointestinal (GI) fluids.

Impact: Since only dissolved drug molecules can be absorbed, this poor solubility leads to low availability for absorption across the intestinal membrane.

- ❖ intestinal first-pass metabolism, which drastically reduces systemic levels of the active compound. Transdermal formulations (especially microneedles or hydrogels) deliver berberine directly into systemic circulation, avoiding the gut and liver metabolism and resulting

2. Poor Absorption

Description: Berberine has low permeability across the intestinal epithelium due to its quaternary ammonium structure, which makes it hydrophilic and less able to diffuse passively.

Impact: Even if dissolved, only a small fraction can cross the intestinal wall to enter the systemic circulation

3. Rapid Metabolism

Description: Once absorbed, berberine undergoes extensive first-pass metabolism in the intestine and liver, primarily via CYP450 enzymes and glucuronidation. Impact: This significantly reduces the amount of parent berberine that reaches systemic circulation.

4. P-Glycoprotein (P-gp) Efflux

Description: Berberine is a known substrate of P-glycoprotein, an efflux transporter highly expressed in the intestinal epithelium.

Impact: P-gp actively pumps berberine back into the intestinal lumen, further reducing its intracellular concentration and absorption.

advantage of transdermal delivery of berberine, including how it specifically addresses the challenges associated with oral administration.

- ❖ Bypasses first-pass metabolism : Oral berberine shows very low bioavailability due to extensive hepatic and

in significantly higher plasma exposure compared to oral routes.

- ❖ Sustained drug release: Transdermal systems (e.g. hydrogels, escinosomes, microneedles) enable controlled, continuous delivery of berberine over extended periods. In vitro permeation through skin-simulating membranes



- showed steady release kinetics over 24 hours, often fitting diffusion-based models (e.g. Korsmeyer–Peppas), supporting sustained and predictable drug levels.
- ❖ Improved patient compliance: Transdermal formats reduce dosing frequency with long-acting patches or sustained release films, minimizing the need for multiple daily doses and improving adherence. They are easy to apply and remove, non-invasive, and can be self-administered without medical

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supervision, further enhancing convenience and compliance.

- ❖ Minimally invasive and localized delivery: Especially via microneedle arrays, berberine can be delivered through the epidermis into the dermis efficiently without pain, and with precise localization to the targeted skin area.
- ❖ This strategy lowers systemic side effects and allows for local therapeutic action (e.g. for skin infections or wound healing) while still achieving systemic absorption when needed.

✓SummaryTable

Advantage	Why it matters for berberine
Bypasses first pass metabolism route	Preserves active drug levels, greatly improving bioavailability over oral routes
Sustain release	Enables steady therapeutic levels, reducing peaks/troughs and dosing frequency
Better compliance	Simple, painless, easy to self-administer with long-acting formats
Minimally invasive and localized Absorption if required	Local targetability (e.g. skin) with low discomfort; still achieves systemic

Specific Formulation Insights

Chitosan hydrogel: Though berberine's lipophilicity limits passive permeation, penetration enhancers like benzalkonium chloride or Tween-80 dramatically improve skin uptake in vitro.

Microneedle arrays (e.g. chitosan microneedles): These enable berberine to

reach both epidermis and dermis layers effectively, confirmed by mass spectrometry imaging studies

Clinical/Preclinical Evidence

A pharmacokinetic study in rats comparing oral berberine, transdermal berberine, and transdermal dihydroberberine found that



transdermal routes (especially with the precursor DHB) achieved much higher berberine plasma levels (AUC) than oral dosing,

1. Nanocarriers

These systems help in enhancing the solubility, stability, and skin permeability of berberine.

a. Liposomes

Structure: Phospholipid bilayer vesicles that encapsulate both hydrophilic and lipophilic drugs.

Benefits: Improved berberine skin penetration and reduced degradation.

Study: Liposome-encapsulated berberine showed increased anti-inflammatory effect and skin permeation.

b. Ethosomes

Structure: Ethanol-rich soft vesicles.

Benefits: Ethanol enhances skin fluidity, allowing deeper penetration.

Use: Increased delivery of berberine through the stratum corneum.

c. Niosomes

Structure: Non-ionic surfactant vesicles.

Advantages: Cost-effective and stable compared to liposomes.

Effectiveness: Improved berberine skin retention and release.

2. Microneedles (MNs)

Mechanism: Create transient microchannels in the skin without pain.

Application: Can deliver berberine directly into the dermis, bypassing the barrier function.

Outcome: Enhanced bioavailability and reduced first-pass metabolism.

3. Gels and Patches

a. Hydrogels

Type: Water-based polymer networks.

Use: Deliver berberine in a sustained-release manner.

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with no adverse effects on liver or kidney biomarkers and no impact on CYP3A4 metabolism of simvastatin.

Advantage: Cooling, soothing effect, and biocompatibility.

b. Organogels

Type: Non-aqueous gels formed by organogelators.

Advantage: Can solubilize hydrophobic berberine, improving its skin delivery.

4. Solid Lipid Nanoparticles (SLN) / Nanostructured Lipid Carriers (NLC)

SLN: Lipid core matrix; NLC: SLN + liquid lipid (improves loading and release)

Use for Berberine:

Enhanced dermal penetration.

Protection from degradation.

Controlled release.

5. Transfersomes and Proniosomes

a. Transfersomes

Structure: Ultra-flexible vesicles with surfactants.

Function: Squeeze through skin pores.

Use: Enhances berberine delivery to deeper skin layers.



b. Proniosomes

Form: Dry formulation that converts to niosomes on hydration.

Advantage: Better stability, easier storage.

Application: Suitable for transdermal berberine systems.

Transdermal drug delivery is an exciting and challenging area. There are numerous transdermal delivery systems currently available on the market. However, the transdermal market still remains limited to a narrow range of drugs. Further advances in transdermal delivery depend on the ability to overcome the challenges faced regarding the permeation and skin irritation of the drug molecules. Emergence of novel techniques for skin permeation enhancement and development of methods to lessen skin irritation would widen the transdermal market for hydrophilic compounds, macromolecules and conventional drugs for new therapeutic indications. As evident from the ongoing clinical trials of a wide variety of drugs for various clinical conditions, there is a great future for transdermal delivery of drugs.

Delivery of drugs through the skin has been an attractive as well as a challenging area for research. Advances in modern technologies are resulting in a larger number of drugs being delivered transdermally including conventional hydrophobic small molecule drugs, hydrophilic drugs and macromolecules. Transdermal systems are a desirable form of drug delivery because of the obvious advantages over other routes of delivery. Transdermal delivery provides convenient and pain-free self-administration for patients. It eliminates frequent dosing administration and plasma level peaks and valleys associated with oral dosing and injections to maintain a constant drug concentration, and a drug with a short half-life can be delivered easily. All this leads to enhanced patient compliance, especially when

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long-term treatment is required, as in chronic pain treatment and smoking cessation therapy. Avoidance of hepatic first-pass metabolism and the GI tract for poorly bioavailable drugs is another advantage of transdermal delivery. Elimination of this first-pass effect allows the amount of drug administered to be lower, and hence safer in hepato-compromised patients, resulting in the reduction of adverse effects. Transdermal systems are generally inexpensive when compared with other therapies on a monthly cost basis, as patches are designed to deliver drugs from 1 to 7 days. The other advantage of transdermal delivery is that multiple dosing, on-demand or variable-rate delivery of drugs, is possible with the latest programmable systems, adding more benefits to the conventional patch dosage forms. The general acceptability of transdermal products by patients is very high, which is also evident from the increasing market for transdermal products.

Conclusion and Perspectives

Berberine is a multifunctional, natural product with therapeutic potential in vascular diseases, including cardiovascular disease, atherosclerosis, hypertension, cerebrovascular disease, diabetes and associated complications, intestinal vascular disease and cancer (Zhu et al., 2018; Martini et al., 2020; Yin et al., 2021). The present review has shown the excellent protective effect of berberine in diverse vascular diseases by preserving vascular endothelial cells, improving vascular remodeling and vasoconstriction, and suppressing inflammation, oxidative stress, autophagy, and apoptosis, based on recent in vitro and in vivo experimental reports (Figure 2). Moreover, berberine also modulates the concentration of Na^+ , Ca^{2+} and lipid metabolism in the VSMCs (Table 4). What is more, the



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network diagram of “vascular diseases-target-pathways” was shown in (Figure 5), and the underlying mechanism of berberine in the treatment of vascular diseases mentioned in this paper may be related to multiple pathways, including HIF-1 α /VEGF, STAT, MAPK, NF- κ B, SIRT, PI3K/Akt, AMPK and TRPV-4.

According to our review, there are still many issues to overcome regarding the use of berberine to treat the vascular diseases. First, the bioavailability of orally-administered berberine in vivo is low due to first-pass elimination. It is therefore imperative to investigate alternative modes and methods of drug delivery with the aim of increasing the bioavailability of berberine. Numerous studies have showed that the strategic use of nanotechnology, including nanocarriers, liposomes, and microfluidic technology-assisted preparation methods, may increase the bioavailability of berberine for use in cardiovascular and metabolic diseases.

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