Novel Perspectives and Insights into the Pharmacological Potential of Berberine for Human Health

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Abstract:

A naturally occurring alkaloid molecule with several health benefits, Berberine is present in many plant sections. It was first used in ancient cultures' traditional Ayurvedic healing procedures. The purpose of this study is to present a summary of recent research on the evolution and enhanced effectiveness of Berberine's curative properties.The process of isolation and potential therapeutic benefits of Berberine are highlighted in this review, along with its prospective application as substitutes for traditional treatments for chronic illnesses like cancer, glucose intolerance, neurological disorders and heart diseases. Berberine has been shown to have potential effects on various disorders in both preclinical and clinical trials. The pharmacological effects of Berberine have been shown in many research works where a good impact of Berberine is reported on a number of physiological processes, such as endothelial function, inflammation, oxidative stress, and the metabolism of fat and glucose.Thus, the information of research currently available indicates that Berberine has medicinal value for a number of pathological disorders. However, further research is needed to determine the most effective dosage, mode of administration, and possible side effects. Furthermore, investigations are required to assess its long- term safety profile and effectiveness, especially when used in conjunction with other medications. Although the majority of current studies yield positive results, more thorough research is still necessary, especially through clinical trials, to confirm its therapeutic safety and effectiveness in treating illnesses.

Keyword: Alkaloid, Berberine, Ayurvedic, Physiological processes.

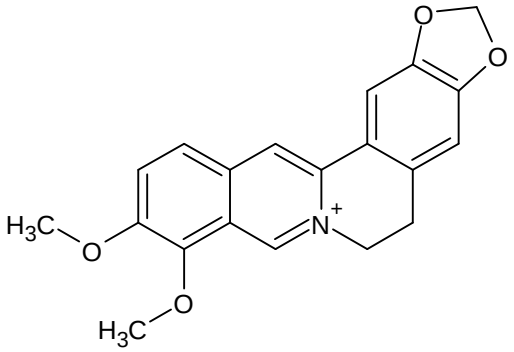
INTRODUCTION

Medicinal plants which are used to counteract diseases, have been playing an important role in the primary health care of humans. They are a potential source of new bio-active substances of wide structural diversity, which can be utilized directly as pharmacologically active compounds or as pro-drugs (Ahmed WJ et al., 2015). In the early 1900's before the start of lead/drug discovery through synthesis, 80% of all active pharmaceutical ingredients were obtained from plant sources (Siddiqui AA et al., 2014).

However, due to the challenging and laborious nature of natural product-based drug discovery and development process, pharmaceutical companies de-emphasized natural product drug discovery since the late 20th century, and advanced technologies namely high-throughput screening and combinatorial chemistry have been introduced to facilitate the discovery of drug leads (Shen B, 2015). However, despite a huge financial incentive that can be obtained from successfully developed and marketed drug products, modern drug discovery and development is also a long and expensive process characterized by low productivity. The high risk of failure in drug discovery and development throughout the pharmaceutical industry statistically shows that, on an average, only 1 in 5000 compounds screened in research will successfully reach the market for clinical application (Gibson M, 2009). Furthermore, the emergence of drug-resistance and cost-ineffectiveness of synthetic drugs are increasing the interest in medicinal natural products-based drug discovery (Amritpal S et al., 2010). The utilization of natural products as a safer, better efficacy, and cost-effective therapeutic alternative is thus of paramount importance. Hence it can be concluded that natural products which are evolutionarily optimized as drug-like molecules remain one of the best sources of drugs and drug leads (Cragg GM, Newman DJ, 2013).

Berberine-containing plants are widely used in various traditional medicine systems such as Ayurveda (India), Traditional Chinese Medicine (China), Tibet and Japan (Nechepurenko I, Salakhutdinov N, Tolstikov G, 2010). In Traditional Chinese Medicine berberine has been used for thousands of years to treat parasitic intestinal infection and bacterial diarrhea (Li D et al., 2017). Moreover, some berberine containing medicinal plants were recorded in the Pharmacopoeia of China (2015) for their therapeutic effects including lowering body temperature, resolving dampness, purging fire and detoxification (Wang K et al., 2017). The use of plants belonging to the genus Berberis was reported in the Indian folk medicine for the treatment of leishmaniasis and malaria and was used in the Japanese folk medicine against cholera and bacterial diarrhea (Nechepurenko I, Salakhutdinov N, Tolstikov G, 2010). It is also reported that the plant species Phellodendronamurense was used in Japan against dysentery and Corydalis was used as an analgesic and spasmolytic agent against a toothache. Besides to its application in traditional medicine systems a growing number of research studies focused on pharmacological activities of berberine against a wide range of diseases, which have attracted the attention of researchers, clinicians and the public, have been conducted to facilitate its future development and clinical application (Habtemariam S, 2016). The various pharmacological activities of berberine result from its direct interaction with nucleic acids and with several proteins (Tillhon M et al., 2012).Berberine is certainly the most significant isoquinoline based alkaloid of protoberberine group. It is mostly isolated from the roots, stems, rhizomes and bark of different plants of Berberis species such as Berberisaristata, Berberis vulgaris, Coptischinensis, Mahoniaaquifolium, Tinosporacordifolia, Eschscholziacalifornica, Hydrastiscanadensis, etc. Berberine in its structure contains one positively charged nitrogen atom at 7 position, two dimethoxy groups in 9,10 position and one methylene dioxy group at 2,3 position of the molecule as shown in Fig I. Berberine is a protoberberine alkaloids are from isoquinoline family of alkaloids and defined as a group of alkaloids containing an isoquinoline or hydroisoquinoline ring system within their structure. In plants, most of the protoberberine alkaloids exist in the form of either tetra-hydroprotoberberines or quaternary protoberberine salts. (Bentley, 2005; Bentley, 2006).

Protoberberine alkaloids are from isoquinoline family of alkaloids and defined as a group of alkaloids containing an isoquinoline or hydroisoquinoline ring system within their structure. In plants, most of the protoberberine alkaloids exist in the form of either tetrahydroprotoberberines or quaternary protoberberine salts. Berberidaceae, Convolvulaceae, Papaveraceae, Annonaceae, Fumariaceae, Menispermaceae, Ranunculaceae, Magnoliaceae and Rutaceae are the known family of plants where the protoberberine alkaloids are distributed (Bentley, 2005; Bentley, 2006). Protoberberine alkaloids perform a significant role in various field of biological and pharmacological application involving protein biosynthesis, inhibition of membrane permeability as well as of DNA synthesis (Schmeller et al., 1997) and the uncoupling of oxidative phosphorylation. These are the processes that likely have vital contribution in the allelochemical and toxic effects against different herbivores and other competing plants. Again, the activities such as interaction with DNA and inhibition in the reverse transcription process are likely to contribute to the inhibition procedure of different viruses. Furthermore, protoberberine alkaloids also offer cytotoxic activity, antitumor property (Kim et al., 1998) as well as in vitro antimalarial activity (McCall et al., 1994).



Structure of berberine

Berberine due to its exciting biological properties has drawn the attention of global researchers only to report its application in biomedical chemistry research. Several reports are already there about its interaction with human platelet alpha-2 adrenergic receptors (Hui et al., 1991), genetotoxicity in prokaryotic and eukaryotic organisms (Pasqual et al., 1993), vasodilatory effects in rat mesenteric artery (Chiou et al., 1991), preventive enzymatic activity against tyrosine hydroxylase (Lee and Zhang, 1996b), potential inhibitory action against telomerase effect on a human leukemic cell line (Meyerson, 2000; Naasani et al., 1999), exultant anti-adipogenic and anti-inflammatory effects on 3T3-L1 adipocytes (Choi et al., 2006), repellent effect on the incursion of human cancer cells (Peng et al., 2006) and in vivo reduction of parasitaemia developed by Plasmodium chabaudi infection in mice. In human malaria Plasmodium falciparum FCR-3 berberine reportedly act as a potent in vitro inhibitor of nucleic acid as well as protein synthesis (Elford, 1986). Kuo et al. through their studies revealed that berberine could cause apoptosis in human leukemia HL-60 (Kuo et al., 1995). Actually, this important alkaloid has become a topic of global research interest for its alluring antibacterial activity, structure activity relationship (Iwasa et al., 1996), antiinflammatory and anti-cancer potential (Kuo et al., 2004), antiarrhythmic effect (Wang et al., 2004), the anticholesterol activity (Kong et al., 2004),

anti-diabetic effect and in vitro antiproliferative activity (Letasiova et al., 2006). In this review the preliminary research studies which have confirmed the therapeutic effect of berberine in the treatment of diseases against which berberine is mainly used in traditional medicine systems including the mechanisms of its action are discussed. Moreover, the pharmacological activity of berberine for the treatment of diseases which are the global leading causes of death such as cardiovascular diseases and cancer is included.

Isolation of Berberine:

1. **Berberine from *Ceriopsdecandra*leaves.**
   Collect and thoroughly dry the leaves containing berberine. Ensure that the leaves are free from contaminants then grind the dried leaves into a coarse powder using a mortar and pestle or grinder. Aim to increase the surface area for extraction then place the powdered leaves in a clean, dry glass container or Erlenmeyer flask, then add a sufficient amount of ethanol to cover the plant material completely. The ratio of plant material to solvent may vary but is typically in the range of 1:5 to 1:10 (w/v). Then seal the container and let it sit in a cool, dark place for an appropriate duration (e.g., 3-7 days). Agitate the mixture intermittently. After maceration, filter the extract through a funnel lined with filter paper or cheesecloth to remove solid plant particles. Collect the filtrate in a clean container. Concentrate the filtrate using a rotary evaporator or distillation apparatus to remove the ethanol. This step is essential to obtain a more concentrated berberine solution. Adjust the pH of the concentrated extract to a slightly acidic or neutral range using pH meter. This step helps in the precipitation of berberine. Allow berberine to precipitate by adding a small amount of water or adjusting the pH. Stir the mixture gently.Separate the precipitated berberine by filtration or centrifugation. Wash the precipitate with water to remove impurities.Dry the isolated berberine in a vacuum oven or desiccator to remove any remaining water. Analyze the isolated berberine using appropriate analytical tools to confirm its identity and purity.
2. **Berberine from the stems of *Cosciniumfenestratum***: Collect the stems of *Cosciniumfenestratum* were used as the starting material and the stems were ground and soaked in methanol (MeOH) for 5 days, repeated three times. The methanolic extract was then acidified to pH2 using concentrated hydrochloric acid (HCl) and filtered to collect a yellow precipitateand the yellow precipitate was recrystallized in methanol to obtain berberine chloride as a yellow powder. The yield of berberine chloride was 4.8%.Characterization of Berberine chloride showed specific NMR (Nuclear Magnetic Resonance) signals indicating its purity and identity.

3. **Berberine from *Berberis vulgaris*:** Firstly, Collect and Prepared of Plant Material and In harvesting, the roots, bark, and stem of Berberis vulgaris are the primary sources of berberine. These parts of the plant are collected, often during specific seasons for optimal alkaloid content. After the harvesting drying and grinding, the plant material is then dried to reduce moisture content, which can facilitate the extraction process. After drying, the material is ground into a fine powder to increase the surface area for extraction.

4.

Pharmacology activity:

1. **The effect of berberine on neurotransmitters in depression:** The exact mechanism of berberine action in depression is not fully understood, but some studies suggest that it may exert its effects through modulation of neurotransmitters such as serotonin (Serotonin is often referred to as the "feel-good" neurotransmitter because of its role in regulating mood. Some research suggests that berberine may increase serotonin levels in the brain by inhibiting the reuptake of serotonin, similar to selective serotonin reuptake inhibitors (SSRIs), which are a class of antidepressant medications), dopamine(Dopamine is involved in the brain's reward system and plays a crucial role in motivation and pleasure. Some studies indicate that berberine may increase dopamine levels in certain brain regions, which could contribute to its antidepressant effects.) And nor-epinephrine (Nor-epinephrine is both a neurotransmitter and a hormone, playing a role in the body's "fight or flight" response. Imbalances in nor-epinephrine levels have been implicated in depression. Berberine may influence nor-epinephrine levels by various mechanisms, including inhibiting its reuptake).
2. **The effect of berberine on Oxidative stress in depression**: Some research suggests that berberine may exert anti-oxidative effects, which could potentially be beneficial in the context of depression.Reduction of oxidative stress(Oxidative stress occurs when there's an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them or repair the resulting damage. Oxidative stress has been implicated in the pathophysiology of depression, as it can damage cells, including neurons, and contribute to inflammation), Inhibition of inflammatory pathways (Inflammation and oxidative stress are closely linked, and both play roles in the development and progression of depression. Berberine has been found to inhibit inflammatory pathways and reduce the production of pro-inflammatory cytokines. By suppressing inflammation, berberine may indirectly reduce oxidative stress, as inflammation can trigger the production of ROS. This dual action on inflammation and oxidative stress may contribute to berberine potential antidepressant effects), Protection of mitochondrial function (Mitochondria are the energy-producing organelles within cells, and they are particularly susceptible to oxidative damage. Dysfunction of mitochondria has been implicated in depression. Berberine has been shown to protect mitochondrial function and promote mitochondrial biogenesis, which could help mitigate oxidative stress and improve cellular energy production in individuals with depression).
3. **The effect of berberine on bipolar affective disorder:** In recent years, prolyl-oligopeptides (POPs) have gained prominence as targets for the treatment of bipolar affective disorder. POP has been reported to participate in the processing of neuropeptide precursors.Moreover, neuroprotective effects of POPs inhibitors have been reported in experimental animals. Berberine inhibits POPs in a dose-dependent manner. However, few studies have reported the effects of berberine in bipolar disorder. As noted below, some neurotransmitters such as dopamine, glutamate, and γ-aminobutyric acid (GABA) are responsible for mood cycling, while, dopamine and glutamate increase transmission during the manic phase. More evidence is required to substantiate a relationship between bipolar affective disorder and berberine.

4. **The effect of berberine on Diabetes:** Berberine has gained attention for its potential benefits in managing diabetes; particularly type 2 diabetes mellitus (T2DM). Berberine has been shown to enhance insulin sensitivity, allowing cells to better respond to insulin and uptake glucose from the bloodstream. This effect is beneficial in T2DM, where insulin resistance is a hallmark feature. And Berberine has demonstrated the ability to lower blood glucose levels by various mechanisms, including increasing glucose uptake by cells, inhibiting glucose production in the liver (gluconeogenesis), and enhancing insulin secretion from pancreatic beta cells. These actions help regulate blood sugar levels, which is essential in diabetes management.
5. **The effect of berberine on Cancer:** Berberine exhibits an anticancer role through scavenging free radicals, induction of apoptosis, cell cycle arrest, inhibition of angiogenesis, inflammation, PI3K/AKT/mammalian target of rapamycin (mTOR), Wnt/β-catenin, and the MAPK/ERK signaling pathway. Induction of apoptosis or programmed cell death, is a natural process that helps to eliminate damaged or abnormal cells, including cancer cells. Berberine has been shown to induce apoptosis in various cancer cell lines, including breast, lung, colon, prostate, and liver cancer cells. It does this by activating certain apoptotic pathways and inhibiting anti-apoptotic proteins .and Berberine can inhibit the proliferation of cancer cells by interfering with various signaling pathways involved in cell growth and division. For example, it can inhibit the activity of certain enzymes such as protein kinases, which are involved in cell signaling and regulation of cell cycle progression. And Chronic inflammation is often associated with cancer development and progression. Berberine has been shown to possess anti-inflammatory properties by inhibiting the production of pro-inflammatory cytokines and enzymes. By reducing inflammation, berberine may help to prevent the initiation and progression of cancer.

6. **The effect of berberine on nitric oxide in depression:** The relationship between nitric oxide (NO) synthesis and depression, particularly with regards to berberine's pharmacological manipulation of this pathway, is complex and multifaceted. The systemic inhibition of nitric oxide synthase (NOS), especially the neuronal form (nNOS), has been shown to induce antidepressant-like effects in the rat hippocampus, suggesting that NO plays a significant role in the modulation of depressive behaviors. By inhibiting nNOS, berberine decreased the immobility time in animal models, a classic sign of antidepressant-like activity. This suggests that berberine can reverse depressive symptoms induced by reserpine, a drug known to deplete monoamine neurotransmitters, thereby inducing a depressive-like state.The pharmacological manipulation of the NO pathway by berberine also points to its interaction with serotonin signaling pathways. Inhibition of nNOS appears to enhance serotonin signaling and activate prosencephalic 5HT1A receptors, which are crucial for antidepressant effects. This connection highlights the intricate balance between different neurotransmitter systems in the regulation of mood and the potential of berberine to modulate these systems therapeutically.Furthermore, the adenosine monophosphate-activated protein kinase (AMPK) pathway plays a critical role in regulating NO synthesis in endothelial cells, with AMPK acting as an upstream kinase of eNOS. Berberine's activation of the AMPK pathway leads to eNOS phosphorylation, promoting NO production. This mechanism underscores the broad physiological impact of berberine, extending beyond the central nervous system to include endothelial function and cardiovascular health.Interestingly, the L-arginine-NO-cyclic

guanosine monophosphate (cGMP) signaling pathway is important in the antidepressant action of berberine chloride. While excessive levels of cGMP can produce a depression-like state, reduced levels are associated with antidepressant-like actions. Berberine's ability to influence this pathway may be another aspect of its antidepressant potential.Overall, the evidence suggests that berberine's effect on the NO pathway, particularly through systemic inhibition of NOS, modulation of serotonin signaling, activation of the AMPK pathway, and influence on the L-arginine-NO-cGMP signaling pathway, contributes to its antidepressant-like effects. This multi-target approach not only provides insights into the complex pathophysiology of depression but also underscores the therapeutic potential of berberine as an antidepressant. However, further research, including clinical studies, is necessary to fully understand the mechanisms through which berberine exerts these effects and to explore its potential application in the treatment of depression.

7. **The effect of berberine on neuroinflammation in depression**: Neuroinflammation refers to the inflammatory response within the brain, characterized by the activation of microglia (the resident immune cells of the brain) and the increased production of pro-inflammatory cytokines. This state of inflammation has been implicated in the development and progression of depression, affecting neurotransmitter systems and brain function. The inflammation model of depression suggests that heightened levels of pro-inflammatory cytokines can disrupt the balance of neurotransmitters, such as serotonin and glutamate, leading to depressive symptoms.

8. **The effect of berberine on anti-inflammatory action**: Berberine exerts anti-inflammatory effects by modulating various cellular signaling pathways and reducing the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1-beta (IL-1β), and tumor necrosis factor-alpha (TNF-α). These cytokines are known to be elevated in depressive states and can affect the brain's neurotransmitter systems. By decreasing the levels of these cytokines, berberine can help mitigate the inflammatory response in the brain.

9. **The effect of berberine on Modulation of Neurotransmitter Systems:** Berberine's impact on neuroinflammation also extends to the modulation of neurotransmitter systems involved in depression. It has been suggested that berberine can influence the serotonergic and glutamatergic systems, which are critical in mood regulation and cognitive functions. Through its anti-inflammatory effects, berberine may prevent the dysregulation of these neurotransmitters, contributing to its antidepressant effects.

10. **The effect of berberine on Inhibition of Indoleamine 2,3-Dioxygenase (IDO):** IDO is an enzyme involved in the metabolism of tryptophan into kynurenine, a pathway activated by inflammation. The activation of this pathway can lead to a reduction in serotonin synthesis (as tryptophan is a precursor) and the production of neuroactive metabolites that may contribute to depressive symptoms. Berberine has been identified as an IDO inhibitor, which could help preserve tryptophan levels, maintain serotonin synthesis, and reduce the production of potentially neurotoxic kynurenine metabolites.

Some analogues of berberine:

I. **Antioxidant Activities:** The radical scavenging activity of the berberine derivatives towards DPPH and ABTS radicals was assessed, showing that compounds with disubstituted piperazine derivatives attached to the berberine nucleus through a pentyl chain enhanced antioxidant effects. Compounds 4h and 4i showed the highest scavenger activity, likely due to the presence of dichloro functionality on the piperazine rings.

II. **Anticancer Activities**: The berberine derivatives demonstrated significant inhibitory effects against the cervical cancer cell line Caski, with compounds 4a–i showing IC50 values ranging from 5.697 to 6.807 µg mL-1, indicating low cytotoxicity towards normal cell lines but excellent inhibitory effects against cancer cell lines. Compound 4h, with a 3,4-dichlorophenyl piperazine entity, was found to be the most active analogue, exhibiting double the potency of the parent berberine

III. **Berberine and Its Derivatives:** Berberine is identified as a potent alkaloid with significant antimicrobial activity against a range of bacteria. Its mechanism involves influencing DNA duplication, RNA transcription, protein synthesis, and the integrity of cell surface structures. This study emphasizes the enhanced efficacy of berberine analogues, suggesting that structural modifications can improve antimicrobial properties.

IV. **Interaction with FtsZ Protein:** The research delves into the interaction between berberine derivatives and the FtsZ protein, a highly conserved protein crucial for bacterial cell division. Specifically, it examines N-arylmethyl benzodioxolethylamines, simplified analogues of berberine, for their ability to inhibit FtsZ's GTPase activity through different mechanisms. The tertiary amine 1c is highlighted as a competitive inhibitor that significantly impacts FtsZ's functionality, suggesting that specific structural changes can enhance the interaction with the enzyme.

V. **Molecular Docking and Inhibitory Mechanisms:** Molecular docking simulations predicted various interactions of berberine analogues with FtsZ, leading to different inhibitory mechanisms. Compounds like 1c, 1d, and 2g,h showed binding to different regions of FtsZ, affecting its GTPase activity and assembly capabilities. This indicates the potential of these analogues to disrupt bacterial cell division by targeting the FtsZ protein.

VI. **Antimicrobial Activity:** The study also tests the in vitro antimicrobial activity of the synthesized berberine analogues against E. coli. The results demonstrate varied minimum inhibitory concentrations (MICs), indicating the potential of these compounds as antibacterial agents. It suggests that differences in lipophilicity and molecular structure can influence a compound's ability to penetrate bacterial cells and exert its inhibitory effect.

In this research provides valuable insights into the development of berberine derivatives as potential antimicrobial agents by targeting the FtsZ protein in bacteria. It highlights the importance of structural modifications to enhance antimicrobial efficacy and suggests new avenues for combating bacterial resistance through the inhibition of bacterial cell division mechanisms.

Conclusion:

Berberine is an isoquinoline alkaloid possessing antibacterial, antioxidant, anti-inflammatory, and anticancer effects. Diabetes and its aftereffects, notably osteoporosis, retinal degeneration, heart disease, kidney failure, neurological disorders, hepatic damage, endothelial dysfunction, and vascular issues, have all been shown to benefit from it. Notably, berberine's impacts on regulating lipid metabolism, controlling intestinal flora, lowering blood sugar, reducing oxidative stress, and inhibiting inflammatory responses are not independent; rather, they reinforce and mutually impact one another.Data from both in vitro and animal models of neurodegenerative disorders indicate the positive benefits of berberine, suggesting that it may be a promising prospective therapeutic target for a variety of neurodegenerative diseases. Additionally, since berberine-containing natural products are widely available, including them into the diet is simple and can be done so as a prophylactic treatment for various life-style disorders.In order to validate the dosage and effectiveness numerous pharmacokinetic investigations are required and to enhance the evidences clinical trials are required to be performed. The semi-synthetic derivative of Berberine has also been studied to some extent and many promising novel analogues have been found. In order to utilise this novel molecule, it is very crucial to collect scientific evidences through pre-clinical, clinical, stability, pharmacokinetic and formulation development studies.

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