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A REVIEW ON PHARMACOLOGICAL ACTIVITIES OF BERBERINE IN HERBAL PLANTS AS TRADITIONAL MEDICINE FOR VARIOUS DISEASES

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ABSTRACT

Herbal plants play a vital and crucial role in everyday life. These plants produce some metabolites called phytochemicals or secondary metabolites. They are biologically active and thus involve in prevention and treatment for various illnesses. The isoquinoline alkaloids family of plant metabolites include berberine, which has potent biological and pharmacological effects. Among these wide range of phytochemicals, Isoquinoline alkaloid possess wide range of compounds. Each compound in this group has multifunctionality in medicine. Due to its anticancer potential based on numerous biochemical pathways, particularly its proapoptotic and anti-inflammatory activity, berberine is currently attracting a lot of attention. The activities of anti-ulcer, anti-diabetic, anti-inflammatory is finding rich source for drug developing. Because of this, it is necessary to summarize the current state of knowledge and research on berberine. This review has focused some of the pharmacological role and potential of berberine, an isoquinoline alkaloids.

Keywords: Berberine, Herbal Plants, Isoquinoline alkaloids, Pharmacology, Phytochemicals.

1. INTRODUCTION

The Modern medicine and drug development have been playing an essential role in the field of pharmaceuticals. Plants have been used as medicine for thousands of years and continue to be used today **(Grover *et al.*, 2002).** Trial and error were initially employed to identify useful plants with advantageous effects, whether it was to treat ailments or simply to feel better. Traditional medicine is a term that refers to the progressive refinement of the use of these plants through many generations **(Kunle *et al.*, 2012).** The use of medications grew throughout time. Direct application of medicinal herbs appears to have been replaced in modern medicine up to this point. As a result, plants are frequently employed as raw materials in the pharmaceutical sector, which produces pharmaceutical drugs that are heavily dependent on plant active principles. Still, however, the poor world lacks access to this modern medication of synthetic origin, and because traditional medicine based on the direct use of medicinal plants is still more affordable, it is still widely used in many parts of the world (Salmerón-Manzano and Manzano-Agugliaro, 2020). In addition to the necessary nutrients for life, plants also contain additional bioactive phytochemicals that help to promote health and prevention of diseases. While it has long been believed that the macro- and micronutrients found in plants are one of the essential elements for human health, phytochemicals have just lately come to light as important cellular signaling pathway modulators **(González-Vallinas *et al.*, 2013).**

Plants produce phytochemicals, also known as secondary metabolites, through a number of different chemical routes. Recent research has shown that a wide range of phytochemicals can be advantageous to the operation of human cells. It is strongly indicated that swallowing these phytochemicals can aid to improve health because numerous research have shown the impact of foods rich in phytochemicals on health **(Mursu *et al.*, 2013).** Several plant species include a wide class of phytochemicals called isoquinoline alkaloids. They are mostly found in the Ranunculaceae, Berberidaceae, and Papaveraceae families and exhibit extraordinary biological activities **(Khan and Suresh Kumar, 2015).** They are essentially generated from the amino acids phenylalanine and tyrosine by reacting the precursor 3,4-dihydroxytyramine (dopamine) with an aldehyde or ketone. This group can be split into two main types based on their structural similarities: simple isoquinolines, which consist of a benzene ring joined to a pyridine ring, and benzylisoquinolines, which have an additional aromatic ring. The protoberberines, protopines, pavines, and aporphines are only a few of the many classes of alkaloids that share structural similarities with the benzylisoquinolines **(Khan and Suresh Kumar, 2015).** The most significance ones of isoquinoline alkaloids include berberine, palmatine, jatrorrhizine, papaverine, morphine, codeine, corydaline, emetine, sanguinarine, and chelerythrine. Many have been used widely in folk medicine.

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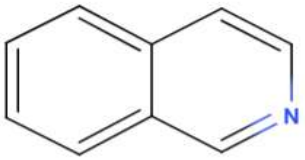

Figure 1: General Chemical Structure of Isoquinoline Moiety

One of the significant molecules in pharmacology and medical chemistry is berberine. This compound is a nonbasic and quaternary benzylisoquinoline alkaloid. Its chemical name is 5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a] quinolizinium. In fact, it is well known as a highly significant natural alkaloid for the condensation, modification, and substitution of functional groups in key places for the design of novel, effective, and selective pharmaceuticals. This results in a variety of bioactive derivatives **(Khan and Suresh Kumar, 2015).**

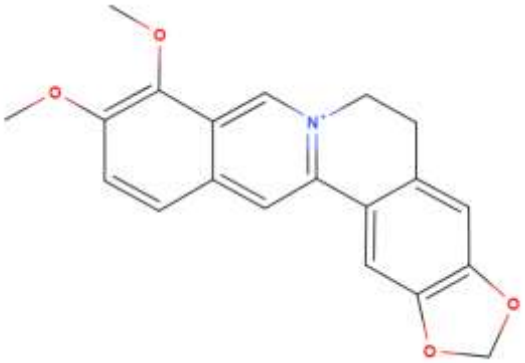

Figure 2: Chemical Structure of Berberine

Berberine has been identified, isolated, and measured in a variety of plant families and genera, including the Annonaceae (*Annickia*, *Coelocline*, *Rollinia*, and *Xylopia*), Berberidaceae (*Berberis*, *Caulophyllum*, *Jeffersonia*, *Mahonia*, *Nandina*, and *Sinopodophyllum*), Menispermaceae (*Tinospora*), Papaveraceae (*Argemone*, *Bocconia*, *Chelidonium*, *Corydalis*, *Eschscholzia*, *Glaucium*, *Hunnemannia*, *Macleaya*, *Papaver*, and *Sanguinaria*), Ranunculaceae (*Coptis*, *Hydrastis*, and *Xanthorhiza*), and Rutaceae (*Evodia*, *Phellodendron*, and *Zanthoxyllum*). The most widely dispersed natural source of berberine is known to come from the species Berberis. More than 8% of the alkaloids found in B. vulgaris' bark are berberine, which accounts for around 5% of the total **(Arayne *et al.*, 2007).**

2. PHARMACOLOGICAL ACTIVITIES OF BERBERINE

Modern pharmacological studies have proved that berberine has abundant biological activities including anti-inflammatory, anti-oxidant, anti-bacterial, viricide, cardiovascular protection, anti-diabetic, anti-ulcer, anti-neurodegeneration, anti- rheumatoid arthritis etc., some of the biological activities of berberine have been discussed briefly.

2.1 Cardiovascular Protection:

According to the findings of Wang *et al.* (2020) **(Wang *et al.*, 2020)**, berberine blocks the PDI-ER stress pathway, which reduces the simultaneous rise in vascular smooth muscle cells proliferation and apoptosis in response to mechanical stretch. It is also reported that the MAPK inhibitors PD98059, SP600125, and SB202190 exhibited additive effects when combined with berberine and significantly inhibited the activation of ERS signalling cascades. The ERS inhibitor 4-PBA decreased MAPK phosphorylation but not PDI activation and ERS signalling. Moreover, berberine reduced the expression of caspase-3 and caspase-12 **(Wang *et al.*, 2020).** Besides, studies shown that increasing the calcium content in cardiac muscle cells may be the mechanism through which berberine improves heart function. In order to increase the inward current carried by calcium ions in the intracellular of cardiac muscle by change of cyclic adenosine monophosphate (cAMP) **(Wang *et al.*, 1994),** cAMP concentration in cardiac muscle cells must be gradually increased. berberine's actions on potassium channels, increased intracellular calcium, and reduced the delay of depolarization which was partly caused by sodium influx led to an increase in high energy phosphate in heart failure and the prevention of ventricular fibrillation **(Wang *et al.*, 1994; Hong *et al.*, 2003).**

2.2 Regulating Blood Lipids:

The lipid-lowering effect of berberine in lipid metabolism appears to be primarily brought on by the extracellular signal-regulated kinase (ERK)-dependent pathway's stabilisation of the hepatic LDL-C receptors (LDLR) as well as

the c-Jun N terminal kinase (JNK) pathway's increased transcriptional activity of the LDLR promoter. Additionally, berberine treatment decreases the levels of leptin in 3T3-L1 cells as well as transcription factors like sterol regulatory element binding protein-1c (SREBP-1c) and CCAAT enhancer-binding protein- (C/EBP-), peroxisome-proliferator activated receptor- (PPAR-), fatty acid synthase, acetyl-coenzyme A (acetyl-CoA) carboxylase, In addition to activating LDLR, berberine also inhibits lipid synthesis by activating 5′ adenosine monophosphate (AMP) kinase (AMPK) and inhibiting the mitogen-activated protein kinase (MAPK)/ERK pathway **(Cao and Su, 2019).**

2.3 Glucose Lowering Effect:

Berberine offers a variety of potential uses and considerable advantages over currently available glucose-lowering medications, which are briefly discussed below: 1) Berberine contains several ways for decreasing blood sugar, including improving insulin resistance, controlling blood sugar and lipid levels, as well as having anti-inflammatory and antioxidant actions **(Li *et al.*, 2021).** Additionally, the recent study by Professor Yang Jinkui's group in 2021 discovered that: 1) Berberine can treat diabetes while minimizing the risk of hypoglycemia by inhibiting the $KCNH_6$ potassium channel; and 2) Berberine can relieve and prevent a variety of diabetic complications, such as diabetic encephalopathy, diabetic nephropathy, and diabetic cardiomyopathy, as well as have a protective effect on the nerves **(Li *et al.*, 2021; Zhao *et al.*, 2021).** Berberine can act as a helpful adjunct in the treatment of type 2 diabetes by making up for the shortcomings of current glucose-lowering medications. In patients with specific insulin synthesis and secretion function in islet cells, sulfonylurea hypoglycemic drugs like glipizide are most effective. However, long-term use of sulfonylureas can result in a decrease in the number and affinity of sulfonylurea receptors on islet G cells, rendering the medication ineffective and increasing the risk of severe hypoglycemia. However, research has revealed that berberine can, to a certain extent, accelerate the regeneration of islet cells and restore islet function **(Xie *et al.*, 2022).** Additionally, research shows that berberine and glipizide work well together because their blood glucose levels are more consistently managed when taken together than when taken separately **(Li *et al.*, 2007).**

2.4 Anti-Breast Cancer Activity:

By attaching to effector proteins, miRNA, and DNA regulatory regions, berberine demonstrated its anti-breast cancer properties by stymieing a variety of cancer-related signals. Notably, several reported molecular targets for berberine in other cancers include receptor retinoid X receptor alpha (RXR), protein tyrosine phosphatase 1B (PTP1B) **(Choi *et al.*, 2015)**, Tumour necrosis factor (TNF) receptor-associated factor 6 (TRAF6), and angiotensin-converting enzyme (ACE); further research is required to determine the functions of these targets in berberine-mediated anti- breast cancer effects. In addition to being able to directly bind to the oncogenes ephrin-B2, SIK3, and LSD1 and inhibit their activity in breast cancer, berberine also had the ability to modify the transcription of a number of genes linked to cancer by physically attaching to their cis-acting regions. Additionally, it has been discovered that berberine blocks a number of signaling pathways to reduce cancer cell invasion and proliferation **(Choi *et al.*, 2015; Ye *et al.*, 2017; Zhong *et al.*, 2022).**

2.5 In Neurodegenerative Diseases:

Numerous preclinical investigations have decisively demonstrated the therapeutic value of berberine in the treatment of a wide range of central nervous system illnesses, including Alzheimer's disease, cerebral ischemia, depression, schizophrenia, epilepsy, and anxiety **(Cheng *et al.*, 2022).** According to a study, berberine helps lessen the cognitive damage brought on by doxorubicin (DOX). In additional research, it was discovered that berberine exerted its antioxidant benefits by downregulating the expression of nuclear transcription factor B (NF-b), apoptotic factors, and pro-inflammatory proteins while upregulating the expression of PGC-1 and manganese superoxide dismutase. To further control synaptic plasticity, berberine can further control the cAMP response element binding protein (CREB) and brain-derived neurotrophic factor (BDNF) **(Cheng *et al.*, 2022; Zhao *et al.*, 2022; Shaker *et al.*, 2021).**

2.6 Hypotensive effects:

By acting as a vasodilator in isolated blood arteries, berberine produces hypotensive effects. During the I/R insult to the heart, coronary artery vasodilation and subsequent coronary flow are crucial. In this situation, berberine improved ventricular fibrillation-affected isolated guinea pig cardiac blood flow. In addition to reducing peripheral vascular resistance and blood pressure, berberine can enhance heart contractility (positive inotropic activity) via raising intracellular calcium levels **(Zhang *et al.*, 2008).** Several mechanisms are proposed for vasodilation and/or hypotensive effect of berberine: the antagonism on α1-adrenoreceptors on VSMCs **(Olmez *et al.*, 1992; Cheng *et al.*, 1987)**, the enhancement of the hypotensive effect of acetylcholine (ACh) on nervus vagus, and thus the inhibition of carotid sinus pressor reflex **(Lau *et al.*, 2001)**; the endothelium-dependent release of NO **(Ko *et al.*, 2000)**; via angiotensin-converting enzyme (ACE) inhibition of the NO-cGMP axis **(Khang *et al.*, 2002)**; the direct activation of K^+ channels in arterial VSMCs leading to hyperpolarization, thereby the inhibition of calcium influx leading to

smooth muscle relaxation **(Lau *et al.*, 2001)**; the inhibition of L- and T-type voltage-gated Ca^{2+} currents in ventricular myocytes **(Xu *et al.*, 1997).**

2.7 Anti-arrhythmic Effect:

Huang *et al.* published the first study on the anti-arrhythmic effects of berberine in 1989 **(Huang *et al.*, 1989).** The authors demonstrated that berberine can stop total ventricular premature beats and ventricular tachycardia by inducing ischemic ventricular arrhythmias in dogs by blocking the LAD coronary artery. ACh-induced atrial fibrillation in rabbits was recently prevented by berberine (2 mg/kg, i.v.) by prolonging the action potential (AP) and the effective refractory time in atrial myocytes. In addition, in isolated myocardial infracted hearts of Wistar rats, berberine (at a dosage of 300 mmol/L) reduced stretch-induced arrhythmia **(Zhou *et al.*, 2015; Jun-xian *et al.*, 2012).** Early research suggested that berberine could prevent class III arrhythmias by inhibiting K^+ channels **(Neto *et al.*, 1993).** However, additional research has shown that berberine targets a variety of channels, including the cardiac slow (IKs) and rapid (IKr) delayed rectifier K^+ channels, the ATP-sensitive K+ channel (KATP), the inwardly-rectifying K+ channel (IKl), the L-type Ca^{2+} channel (ICa), and the human hyperpolarization-activated cyclic nucleotide-gated 4 ($hHCN_4$) channels **(Chen *et al.*, 2014).** In rat ventricular tissues, berberine (10, 20 mg/kg, p.o.) reduced IKr channel expression. berberine also prevented hERG channel expression in hERG-transfected HEK293 cells **(Wei *et al.*, 2013).**

2.8 Transcription Regulation:

Berberine shows activity against the crucial transcription factor 1 (AP-1), which is strongly linked to the development of cancer. AP-1 is composed of complexes that contain the DNA-binding proteins from the Fos family (c-Fos, Fra-1, FosB, and Fra-2), Jun family (c-Jun, JunD, JunB, and v-Jun), ATF/cyclic AMP-responsive element-binding (b-ATF, ATF1-4, ATF-6, and ATFx), and Maf family (c-Maf, MafA, MafB, Ma Growth factors, infections, cytokines, UV radiation, or cellular stress are a few examples of the things that can control AP-1 activity **(Gazon *et al.*, 2018).**

3. CONCLUSION

In this review, we have summarized some of the pharmacological potential and roles of berberine. Due to its shown biological action, particularly in biochemical pathways crucial for apoptosis, carcinogenesis, and metastasis, berberine is one of the most intriguing and promising natural agents available today. Berberine exhibits high effectiveness in the treatment of many clinical stages, such as metabolic diseases and related symptoms, inflammation and its side effects, or cancer prevention and combination cancer treatment, as a natural molecule with low toxicity towards healthy cells. There are restrictions on berberine's biodistribution, absorption, and dissolution, though. In order to get around the drug's limits in clinical use, berberine research is currently focusing a lot on developing novel formulations and derivatives.

STATEMENT OF CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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