BERBERINE A POTENT SUBSTANCE FOR RESEARCHER: A REVIEW

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ABSTRACT
Berberine is a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids. It is present in roots and stem-bark of Berberis species. Berberine has been isolated from various plant families including some are given as Papaveraceae, Berberidaceae, Fumariaceae, Menispermaceae, Ranunculaceae, Rutaceae, and Annonaceae. The alkaloid berberine has a tetracyclic skeleton derived from a benzyl tetrahydroisoquinoline system with the incorporation of an extra carbon atom provided by S-adenosyl methionine (SAM) via an N-methyl group. As a traditional medicine or dietary supplement, berberine has shown some activity against fungal infections, Candida albicans, yeast, parasites, and bacterial/viral infections. Its activity in carbohydrate and lipid metabolisms, diabetes mellitus treatment, endothelial function and the cardiovascular system has been investigated in the last decade with interesting results both in animals and clinical studies. These accumulated data may be helpful for its future research and important study of about berberine.

KEYWORDS: Berberine, Antidiabetic, Isoquinoline alkaloids.

INTRODUCTION
Medicinal plants have been identified and used throughout human history. Plants have the ability to synthesize a wide variety of chemical compounds that are used to perform important biological functions, and to defend against attack from predators such
as insects, fungi and herbivorous mammals. Chemical compounds in plants mediate their effects on the human body through processes identical to those already well understood for the chemical compounds in conventional drugs; thus herbal medicines do not differ greatly from conventional drugs in terms of how they work. This enables herbal medicines to be as effective as conventional medicines, but also gives them the same potential to cause harmful side effects. The use of herbs to treat disease is almost universal among non-industrialized societies, and is often more affordable than purchasing expensive modern pharmaceuticals.

The World Health Organization (WHO) estimates that 80 percent of the population of some Asian and African countries presently use herbal medicine for some aspect of primary health care. Studies in the United States and Europe have shown that their use is less common in clinical settings, but has become increasingly more in recent years as scientific evidence about the effectiveness of herbal medicine has become more widely available. The annual global export value of pharmaceutical plants in 2011 accounted for over US$2.2 billion. All plants produce chemical compounds as part of their normal metabolic activities. These phytochemicals are divided into (1) primary metabolites such as sugars and fats, which are found in all plants; and (2) secondary metabolites compounds which are found in a smaller range of plants, serving a more specific function. For example, some secondary metabolites are toxins used to deter predation and others are pheromones used to attract insects for pollination. It is these secondary metabolites and pigments that can have therapeutic actions in humans and which can be refined to produce drugs examples are inulin from the roots of dahlias, quinine from the cinchona, morphine and codeine from the poppy, and digoxin from the foxglove. Toxic plants even have use in pharmaceutical development.

Alkaloids are a group of naturally occurring chemical compounds that contain mostly basic nitrogen atoms. This group also includes some related compounds with neutral and even weakly acidic properties. Some synthetic compounds of similar structure are also attributed to alkaloids. Alkaloids are produced by a large variety of organisms, including bacteria, fungi, plants, and animals are part of the group of natural products (also called secondary metabolites). Many alkaloids can be purified from crude extracts by acid-base extraction. Many alkaloids are toxic to other organisms. They often have pharmacological effects and are used as medications, as recreational drugs, or in entheogenic rituals.
Isoquinoline is a heterocyclic aromatic organic compound and it is a structural isomer of quinoline. Isoquinoline and quinoline are benzopyridines, which are composed of a benzene ring fused to a pyridine ring. In a broader sense, the term isoquinoline is used to make reference to isoquinoline derivatives. Isoquinoline is a colourless hygroscopic liquid at room temperature with a penetrating, unpleasant odour. Impure samples can appear brownish, as is typical for nitrogen heterocycles. The isoquinoline alkaloids are a large class of medicinally active alkaloids whose properties are variable. Their properties include being antispasmodic, antimicrobial, anti-tumour, antifungal, anti-inflammatory, cholagogue, hepatoprotective, antiviral, amoebicidal, anti-oxidant and can act as enzyme inhibitors.

Berberine is a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids. Berberine is an isoquinoline alkaloid, present in roots and stem-bark of Berberis species. Berberine has been isolated from various plant families including Menispermaceae, Ranunculaceae, Rutaceae, Annonaceae, Papaveraceae, Berberidaceae and Fumariaceae.

The alkaloid berberine has a tetracyclic skeleton derived from a benzyl tetrahydroisoquinoline system with the incorporation of an extra carbon atom provided by S-adenosyl methionine (SAM) via an N-methyl group. Formation of the berberine bridge is readily rationalized as an oxidative process in which the N-methyl group is oxidized to an iminium ion, and a cyclization to the aromatic ring occurs by virtue of the phenolic group.

Berberine based formulations, are widely used in traditional systems of medicine including, Ayurveda and Traditional Chinese Medicine. It is commonly found in the roots, rhizomes, and stem bark of plants. Although alkaloids are normally alkaline and colourless, berberine is acidic in nature and identifiable by its bright yellow colour. Historically it has been used as a yellow dye in a number of countries.
Its activity in carbohydrate and lipid metabolisms, diabetes mellitus treatment, endothelial function and the cardiovascular system has been investigated in the last decade with interesting results both in animals and clinical studies.

As a traditional medicine or dietary supplement, berberine has shown some activity against fungal infections, *Candida albicans*, yeast, parasites, and bacterial/viral infections. Berberine seems to exert synergistic effects with fluconazole even in drug-resistant *C. albicans* infections.

Berberine is considered as antibiotic when applied *in vitro* and in combination with methoxyhydnocarpin, an inhibitor of multidrug resistance pumps. Berberine inhibits growth of *Staphylococcus aureus* and *Microcystis aeruginosa*, a toxic cyanobacterium.

Berberine is a component of some eye drop formulations. There is some evidence it is useful in the treatment of trachoma.

### List of plants contain Berberine

<table>
<thead>
<tr>
<th>Latin name</th>
<th>Common name</th>
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<tbody>
<tr>
<td><em>Argemone</em> species (<em>Tinosporacordifolia, Argemone mexicana</em>)</td>
<td>Prickly poppy</td>
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<tr>
<td><em>Chelidonium</em> species</td>
<td>Celandine poppy</td>
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<tr>
<td><em>Corydalis</em> species</td>
<td>Fitweed</td>
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<tr>
<td><em>Dicentra</em> species</td>
<td>Dutchman’s breeches</td>
</tr>
<tr>
<td><em>Eschscholzia californica</em></td>
<td>Californian poppy</td>
</tr>
<tr>
<td><em>Papaver</em> species</td>
<td>Poppy</td>
</tr>
<tr>
<td><em>Sanguinaria</em> species</td>
<td>Bloodroot</td>
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<tr>
<td><em>Hydrastis canadensis</em></td>
<td>Goldenseal</td>
</tr>
<tr>
<td><em>Coptis chinensis</em></td>
<td>Coptis or goldenthread</td>
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<tr>
<td><em>Berberis aquifolium</em></td>
<td>Oregon grape,</td>
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<tr>
<td><em>Berberis vulgaris</em></td>
<td>Barberry</td>
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<tr>
<td><em>Berberis aristata</em></td>
<td>Tree turmeric</td>
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<tr>
<td><em>Xanthorrhiza simplicissima</em></td>
<td>Yellow root</td>
</tr>
<tr>
<td><em>Phellodendron amurense</em></td>
<td>Amur cork tree</td>
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</table>

### MECHANISM OF ACTION

The pharmacologic actions of berberine include metabolic inhibition of certain organisms, inhibition of bacterial enterotoxin formation, inhibition of intestinal fluid accumulation and ion secretion, inhibition of smooth muscle contraction, reduction of inflammation, platelet aggregation inhibition, platelet count elevation in certain types of thrombocytopenia, stimulation of bile and bilirubin secretion, and inhibition of ventricular tachyarrhythmias.
Molecular mechanism of carbohydrate metabolism

The role of BBR in glucidic metabolism is well established. BBR has been used extensively in the treatment of type 2 diabetes mellitus, and many clinical studies are reported on the hypoglycaemic action of BBR in the Chinese literature. Insulin resistance is a major metabolic abnormality leading not only to type 2 diabetes, but also to a group of metabolic disorders known as the metabolic syndrome.

1. In 2006, Lee et al investigated the mechanisms underlying the effects of BBR in the treatment of diabetes and obesity and on insulin resistance. They showed that BBR acted and stimulated adenosine mono-phosphate kinase (AMPK), and exerted its effects on diabetes and obesity.

The mechanistic basis of BBR action was detected in the expression of genes involved in energy metabolism. BBR down regulated the expression of genes involved in lipogenesis and upregulated those involved in energy expenditure in adipose tissue and in muscle.

The expression levels of 11β-hydroxysteroid dehydrogenase, which is a key enzyme linked to visceral obesity and metabolic syndrome, decreased, along with the expression of most genes involved in carbohydrate metabolism. In contrast, the transcript level of enzymes related to energy dissipation, including glycerol kinase and acyl-CoA dehydrogenase, increased. These results implied that BBR treatment in vivo resulted in a modulation of the gene expression profile that would promote catabolism of high energy intermediates.

2. Others mechanisms involved in BBR actions were clarified by Zhou et al (2008). They reported that BBR promotes glucose uptake in 3T3-L1 preadipocytes through a mechanism distinct from insulin. BBR induced glucose transport by activating GLUT1 and particularly increased glucose transport by enhancing GLUT1 gene expression. This occurs via activation through AMPK. This is in contrast to the action of insulin which increases the uptake of glucose by promoting expression of GLUT4 receptors on cell surface through activation of PI3K.

AMPK activation results in an increase in the uptake of glucose from the blood to target organs. Further, AMPK inhibits the accumulation of fat by modulating down-stream-signaling components like acetyl CoA carboxylase (ACC). AMPK inhibits ACC activity by direct phosphorylation, which leads to a blockage of fatty acid synthesis pathways.
ACTIVATION OF AMPK BY BBR

It was observed that BBR reduced oxygen-dependent glucose oxidation through inhibition of the respirator mitochondrial complex. In this study observe that reduction in aerobic respiration, glycolysis was increased, this pathway requires more glucose than aerobic respiration for producing same amount of ATP. This resulted in increase in glucose uptake and its utilization, and was also associated with a persistent elevation in the AMP/ATP ratio, which induced the activation of AMPK. These data highlighted that the major target of BBR is the complex I of the mitochondrial respiratory chain and it leads to activation of AMPK.

MECHANISM OF THE EFFECT OF BBR ON INSULIN SENSITIVITY

BBR exerts its effect on insulin sensitivity by increasing the expression of insulin receptor (InsR). This effect is dose and time dependent. Increase in the expression of the receptor results in increase in cellular glucose consumption only in the presence of insulin.

ACTIVATION OF INSR THROUGH BBR

BBR induces InsR gene expression, with a mechanism of transcriptional regulation through protein kinase C (PKC). According to recent study In type 2 diabetic mice, treatment with BBR lowered fasting blood glucose and fasting serum insulin, increased insulin sensitivity and elevated InsR mRNA, as well as PKC activity in the liver. The same results were obtained in a variety of human cell lines and were confirmed in a randomized clinical trial, in which BBR treatment significantly lowered fasting blood glucose, hemoglobinA1c, TG and insulin levels in patients with type 2 diabetes mellitus but other studied showed that the activity of BBR acted by the up-regulation of InsR in type 2 diabetes mellitus patients and this effect can be correlated in relationship with the glucose-lowering effect.

The insulin-sensitizing and glucose lowering mechanism of BBR is very suitable in treating insulin resistant and diabetic patients with obesity. This is because BBR was shown to reduce the expression levels of peroxisome proliferator activated receptor γ, suppresses the differentiation of pre adipocytes and reduces the accumulation of lipid droplets.

The therapeutic properties of BBR, namely reducing fasting blood glucose, haemoglobin A1c, and insulin levels in patients with type 2 diabetes mellitus, reduction of fat mass and TG, improvement of insulin resistance, and reduction of body weight, makes it a promising molecule for future development in the treatment of glucidic disorders.
MOLECULAR MECHANISM OF LIPID METABOLISM

The main properties of BBR were initially concentrated on lipid metabolism. It was approved as a nutraceutical substance for treatment of hyperlipidemia in many countries.
In 2004, Kong et al defined BBR as “a new cholesterol-lowering drug”. They demonstrated in vitro and in vivo the efficacy of this substance in lipid lowering, which was comparable to that of statins.

1. **BBR induced expression of LDLR by stabilizing mRNA.**

In vitro studies in human HepG2 cell lines showed that BBR increases the expression of LDLR (low density lipoprotein receptor) gene at a post transcriptional level. This increase was dose and time dependent. The underlying mechanism was stabilization of the LDLR mRNA via activation of the extracellular signal-regulated kinase pathway. This mechanism was distinct from statins, and this activity was totally independent of intracellular cholesterol levels and has no effects on the activation process of the sterol-regulatory element binding protein (SREBP) or the activity of hydroxymethylglutaryl CoA reductase.

These findings translated into clinical results, and, in fact, BBR administration in hypercholesterolemic patients led to a significant cholesterol reduction, which was also evident in animal studies.

The mechanism elucidated by Brusq et al. demonstrated that BBR via AMPK activation inhibited cholesterol and TG synthesis in hepatic cells. The LDLR upregulation, AMPK activation and lipid synthesis inhibition were abolished when the MAPK/extracellular signal regulated kinase (ERK) pathway was blocked.

Abidi et al further demonstrated the BBR-induced stabilization of LDLR mRNA is mediated by the ERK signaling pathway through interactions of the cis-regulatory sequences of the 3-untranslated region of the LDLR mRNA and mRNA binding proteins that are downstream effectors of this signaling cascade. Moreover, it was identified that the LDLR mRNA untranslated region was the target of BBR action leading to LDLR-mRNA stabilization.

2. **Mechanism indicating the action of BBR on the pro-protein convert as esubtilisin/kexin type 9 (PCSK9).**

PCSK9 generally worked by down-regulating, post-transcriptionally, LDLR by shuttling it to the lysosomes for degradation. This increases the level of circulating LDL-cholesterol (LDLc). BBR acts by decreasing PCSK9 mRNA and protein levels in a type and dose dependent manner, likely due to a decreased transcription of the PCSK9 gene.
Thus, BBR could have dual actions on LDLR metabolism by prolonging its mRNA half-life as well as directly increasing protein abundance through the blockage of PCSK9-mediated degradation. The mechanisms underlying the transcriptional suppression of PCSK9 by BBR have been recently clarified in an in vitro study on HepG2 cells.

Li et al identified a highly conserved hepatocyte nuclear factor 1 (HNF1) binding site as a critical sequence motif for PCSK9 transcription. BBR leads to reduction of the TFs- HNF1 and nuclear SREBP2 that result in a strong suppression of PCSK9. Thus BBR act by increasing LDLR expression and stability.

3. Action of BBR on lipid synthesis
BBR effects on lipid synthesis are mediated by the ERK pathway. AMPK phosphorylates and inactivates ACC, a key enzyme involved in fatty acid synthesis, leading to an increase in fatty acid oxidation, decrease in fatty acid synthesis and TG synthesis inhibition. This action of BBR leading to AMPK activation is a valuable approach to target lipid disorders.

Several studies have shown that a combination therapy of BBR with other plant sterols (policosanols and red yeast rice) result in improved cholesterol lowering efficacy through synergistic action on cholesterol adsorption and reduced plasma levels. Such nutraceutical combination can be used to treat dislipidemic patients, and showed significant reduction in total LDLc and TG. The intriguing mechanisms involved in glucidic and lipidic metabolism support BBR efficacy in treating metabolic disorders with a significant safety profile.

Molecular mechanism of BBR action on the endothelium and the heart
Endothelial dysfunction is an important early event in the pathogenesis of atherosclerosis. The mechanisms underlying endothelial injury are numerous and linked to metabolic alteration. In obesity and insulin resistance, the increased secretion of proinflammatory cytokines and decreased secretion of adiponectine, the increased circulating levels of free fatty acids, and hyperglycaemia may alter gene expression and cell signalling in the vascular endothelium. This leads to changes in the release of endothelium derived factors.
Dysfunctional endothelium is characterized by activation of NADPH oxidase, uncoupling of endothelial nitric oxide synthase (eNOS), increased expression of endothelin-1, an imbalance between the production of vasodilators and vasoconstrictor mediators, and induction of adhesion molecules. The altered endothelial homeostasis, in turn, contributes to plaque initiation and progression. It is associated with most cardiovascular disease, such as hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes and chronic renal failure.

In case of hypercholesterolemia the endothelial cells have low capacity to release endothelium derived relaxing factors. The circulating LDL promotes circulating eNOS down regulation. Lowering cholesterol levels appears to improve endothelial function.

In case of diabetes and insulin resistance, other mechanisms may trigger endothelial dysfunction. Insulin signaling is altered in these two conditions, and affects the pathway leading to phosphorylation and activation of eNOS, which is also, in this case, dramatically down regulated. eNOS represents a major weapon of endothelial cells to fight vascular
disease. It generates nitric oxide (NO), whose role is to dilate blood vessels and maintain vascular homeostasis by stimulating cGMP. Several studies have suggested a central role of endothelial AMPK in maintaining physiological functions, such as mediation of eNOS activation in response to shear stress, modulation of endothelial cell energy supply, protection from apoptosis and regulation of inflammation, angiogenesis, and maintenance of perfusion.

Impairment of endothelium dependent relaxation (EDR) represents reduced eNOS derived NO bioavailability, and is the first step in endothelial injury.

In 2000, Ko et al, by *in vitro* investigation, demonstrated that BBR has not only vasorelaxant but also anti proliferative effects. BBR was shown to act on both the endothelium and on the underlying vascular smooth muscle cells to induce relaxation. NO, is likely involved in the EDR. Recent studies confirmed that the vasodilatant effect of BBR was mediated by eNOS leading to NO production through activation of the AMPK cascade.

![Diagram](image.png)

**Fig. 5:** Most metabolic and vascular effects of BBr are mediated by the activation of the AMPK cascade.
Furthermore, BBR suppresses the activation of the nuclear factor-κB (NF-κB), the expression of adhesion molecules (VCAM-1 and ICAM-1) induced by hyperglycaemia and the high glucose-induced elevation of several pro-inflammatory cytokines and chemokines, including tumor necrosis factor-α, IL1-β, IL8 and MCP1, which are other targets of NF-κB involved in the development of atherosclerotic plaques.

Studies by Hong et al, in Sprague-Dawley rats with a supra-renal abdominal aorta constriction, demonstrated efficacy of BBR in modulating the sympathetic nervous activity of rats with experimental cardiac hypertrophy, and may support the therapeutic potentials of BBR in patients with cardiac hypertrophy and chronic heart failure.

Zeng et al investigated the efficacy and safety of BBR administration in patients with congestive heart failure (CHF) secondary to ischemic or idiopathic dilated cardiomyopathy. It was observed that during long term follow-up, total mortality was significantly lower in the BBR treated patients than in the placebo group, due to decrease in sudden cardiac death and death due to CHF.

The antiarrhythmic effect of BBR and its metabolites (tetra-hydro-berberin and 8-oxo-berberin) was shown to modulate multiple ion channels both in sarcolemma and the sarcoplasmatic reticulum. Complex mechanisms as the basis of the antiarrhythmic activity have been demonstrated in vivo in several animal models. These observations make BBR a promising antiarrhythmic agent with the potential to prevent sudden cardiac death.

Although BBR is used most commonly as a traditional medicine, however the recent findings and extensive research have provided novel mechanisms that make BBR a promising tool to counteract metabolic and cardiovascular disorders. It demonstrated effects on the AMPK cascade, involved in CV disorders and metabolic pathways. This proposes BBR as a new therapeutic agent in the treatment of type 2 diabetes and metabolic syndrome.

Overall bioavailability of Berberine is quite low at 'less than 5%' with 0.68% having been reported in rats. Studies using 1,000-1,500mg Berberine by itself still appear to exert benefits after absorption, but enhancing absorption theoretically can reduce the dose of Berberine required to reach these effects. Berberine has low rates of absorption when taken orally due to both being subject to P-Glycoprotein (ejets Berberine back into the intestines) and increasing the activity of P-Glycoprotein (augmenting its own ejection), but absorption is
greatly increased when taken with P-Glycoprotein inhibitors such as Silymarin from Milk Thistle. Absorption has also been enhanced with Sodium Caprate, a medium chain fatty acid. Sodium Caprate, an ester of Capric Acid (Decanoic Acid; a constituent of milk fat at 2-3% and Coconut Oil at 10%) appears to enhance absorption via reversibly widening the gaps between intestinal cells and allowing passive diffusion. It is theoretical, but not yet demonstrated, that coinigestion of Berberine with food sources of Capric acid could increase absorption of Berberine (and assuming 10% Capric acid content of Coconut oil, it is about 5.5g of Coconut oil for a 150lb human). Due to low intestinal uptake rate, large doses (1g) are associated with constipation. Low absorption may precede intestinal side-effects with high doses, due to large colonic levels.

Berberine should not be used during pregnancy as it may cause uterine contractions and miscarriage. It has also been linked to neonatal jaundice. Berberine in very large doses for more than 4-6 weeks may cause liver overload. However doses of 200-1200mg have been found to be safe for most patients.

EXCRETION

Fig 6: Most urinary excretion of Berberine appears to be Jatrorrhizine, with all metabolites having at least once been detected in sulfated or glucuronidated form.

Orally ingested Berberine (chloride) at 900mg daily for 3 days was metabolized into three different urinary metabolites, with one (thought to be Jatrorrhizine-3-Sulfate) being the primary metabolite being excreted at 15-125 times more than the other two metabolites (Demethylenberberine-2-sulfate and Thalifendine-10-sulfate, Berberrubine being
undetectable in urine). A later study noted that 900mg (3x300mg) for two days noted that Jatrorrhizine can be detected in the urine as a glucuronide (jatrorrhizine-3-O-β-D-glucuronide) as can Thalifendine (thalifendine-10-O-β-D-glucuronide), Berberrubine (berberrubine-9-O-β-D-glucuronide), and Demethyleneberberine (demethyleneberberine-2,3-di-O-β-D-glucuronide).

One other metabolite has been found, columbamine-2-O-β-D-glucuronide both Jatrorrhizine and Columbamine can be found naturally occurring in *Enantiachlorantha*.

**PHARMACOLOGICAL ACTION OF BERBERINE**

Berberine extracts and decoctions have demonstrated significant antimicrobial activity against a variety of organisms, including bacteria, viruses, fungi, protozoans, helminths, and chlamydia. Currently, the predominant clinical uses of berberine include bacterial diarrhoea, intestinal parasite infections, and ocular trachoma infections. The root extract of the plant was used as a purgative and blood purifier.

1. **Update on Berberine in Nonalcoholic fatty liver disease**

Yang Liu et al evaluated the non-alcoholic fatty liver diseases that Berberine (BBR), an active ingredient from nature plants, has demonstrated multiple biological activities and pharmacological effects in a series of metabolic diseases including non alcoholic fatty liver disease (NAFLD). The recent literature points out that BBR may be a potential drug for NAFLD in both experimental models and clinical trials. This review highlights important discoveries of BBR in this increasing disease and addresses the relevant targets of BBR on NAFLD which links to insulin pathway, adenosine monophosphate-activated protein kinase (AMPK) signaling, gut environment, hepatic lipid transportation, among others. Developing nuanced understanding of the mechanisms will help to optimize more targeted and effective clinical application of BBR for NAFLD.

2. **Anti-Proliferative and anti-migratory activity**

Liang, et al., 2008, Berberine is capable of inhibiting growth and endogenous platelet-derived growth factor synthesis in vascular smooth muscle cells after *in vitro* mechanical injury. A study, analyzed the effects of berberine on vascular smooth muscle cell growth, migration, and signaling events after exogenous platelet-derived growth factor stimulation *in vitro* in order to mimic a post-angioplasty platelet-derived growth factor shedding condition. The
observations offer a molecular explanation for the anti-proliferative and anti-migratory properties of berberine.

3. **Antimicrobial activity and Antibacterial activity**

*Sack, et al 1982* studied that in one experiment; berberine hydrochloride reduced the cholera toxin-induced secretion of water, sodium and chloride in perfused rat ileum. Berberine was also found to inhibit the intestinal secretory response of *Vibrio cholera* and *Escherichia coli* enterotoxins without causing histological damage to the intestinal mucosa.

*Sun, et al 1988* studied Berberine is also active against other intestinal infections that cause antidiarrhea such as *Shigella dysenteriae*, *Salmonella Paratyphi* and various *Klebsiella species*. Berberine sulphate has been shown to block the adherence of *Streptococcus pyogenes* and *E. coli* to host cells, possibly explaining its mechanism of action against numerous pathogens.

*Gentry, 1998, et al*, Berberine was found to be the active constituent in an extract of *Hydrastis canadensis* root that demonstrated activity against a multiple drug resistant strain of *Mycobacterium tuberculosis*.

Yan, et al., 2007, the growth thermogenic curves of *Escherichia coli* affected by berberine, coptisine (fig. and palmatine (fig 3) extracted from *Coptis chinensis* were determined quantitatively by microcalorimetry. The power-time curves of E. coli with and without the three protoberberine alkaloids were acquired; meanwhile the extent and duration of inhibitory effects on the metabolism were evaluated by growth rate constant (k), half-inhibitory ratio (IC50), peak time of maximum heat-output power (tp), total heat-production (Qt) and so on. The inhibitory effects of three protoberberine alkaloids on E. coli revealed that the sequence of their antimicrobial activity was berberine>coptisine>palmatine.

![Chemical structure of palmitine](image-url)
Wagner et al 2000 Antibacterial activity of berberine is potentiated by methoxyhydnocarpin. This observation has led to the possibility that plants produce both antibacterial compounds and compounds, which target bacterial efflux mechanisms, to inhibit possible resistance to latent plant antibacterial in bacteria in their environment.

4. Ocular Trachoma Infections
A clinical study of aqueous berberine versus sulfacetamide for the treatment of *Chlamydia trachomatis* infection was conducted on 51 subjects in an outpatient eye clinic. It was determined that while sulfacetamide eye drops produced slightly better clinical results, conjunctival scrapings of these patients remained positive for the infective agent, and relapses occurred. In contrast, the conjunctival scrapings of patients receiving berberine chloride eye drops were negative for *C. trachomatis* and there were no relapses, even one year after treatment. It was also concluded that, while berberine chloride had no direct anti-chlamydial properties, it seemed to cure the infection by stimulating some protective mechanism in the host. A second clinical study found berberine chloride superior to sulfacetamide in both the clinical course of trachoma and in achieving a drop in serum antibody titers against *C. trachomatis*.

5. Hepatoprotective activity
Xing, et al., 2009, studied that Hepatoprotective effect of Coptidis rhizoma aqueous extract and its possible mechanism in rats intoxicated with carbon tetrachloride (CCl4) in the present study. Sprague-Dawley (SD) rats aged 7 weeks old were intraperitoneally injected with CCl4 at a dose of 1.0 ml/kg as a 50% olive oil solution. The rats were orally given the Coptidis rhizoma aqueous extract at doses of 400, 600, 800 mg/kg and 120 mg/kg berberine body weight after 6 h of CCl4 treatment. At 24 h after CCl4 injection, samples of blood and liver were collected and then biochemical parameters and histological studies were carried out. The results showed that Coptidis rhizoma aqueous extract and berberine inhibited significantly the activities of alanine aminotransferase and aspartate aminotransferase and increased the activity of superoxide dismutase. The study demonstrated that Coptidisrhizoma aqueous extract has hepatoprotective effect on acute liver injuries induced by CCl4.

6. Antidiarrhoeal activity
Diarrhoea caused by Vibrio cholera and E. coli has been the focus of numerous studies on berberine, and results indicate several mechanisms that may explain its ability to inhibit
bacterial diarrhoea. Berberine has been found to reduce the intestinal secretion of water and electrolytes induced by cholera toxin.

Other studies have shown that berberine directly inhibits some V. cholera and E. coli enterotoxins significantly, reduces smooth muscle contraction, intestinal motility and delays intestinal transit time in humans. In vitro study indicates that berberine sulfate inhibits bacterial adherence to mucosal or epithelial surfaces, which is the first step in the infective process. This may be a result of berberine’s inhibitory effect on fimbrial structure formation on the surface of the bacteria. Another study in mice has shown that berberine has some activity against E. histolytica this makes it useful against bilious disorders.

7. Antiprotozoal activity
Berberine extracts and salts have demonstrated growth inhibition of Giardia lamblia, Trichomonas vaginalis and Leishmania donovani. The crude extracts of berberine have shown to be more effective than its salts. In a clinical trial, berberine administration improved gastrointestinal symptoms and resulted in a marked reduction in Giardia positive stools and it was effective at half the dose of the popular giardiasis medication, metronidazole. A study has shown the drug’s ability to markedly inhibit parasitic load and rapidly improve hematologic parameters in infected animals.

In vitro results indicate that the drug has the ability to suppress organism maturation through inhibition of its multiplication, respiration and macromolecular biosynthesis of amastigote forms of the parasite, and interference with nuclear DNA of the promastigote form. A randomized clinical trial in 215 patients has shown that pyrimethamine effect on chloroquine-resistant malaria was increased more by berberine (74%) than by tetracycline (67%) or cotrimoxazole (48%), which also indicates its antimalarial activity.

8. Mechanisms involved in the cytotoxic effects of berberine on human colon cancer HCT-8 cells
LI-NA XU et al 2012 studied the cytotoxicity of berberine on HCT-8 cancer cells was investigated by MTT assay, fluorescence microscopy and flow cytometry analysis. Our data revealed that berberine could significantly inhibit the growth of HCT-8 cells in a dose- and time-dependent manner. We also found that berberine-induced apoptosis was associated with an up regulated expressions of p53 and prohibiting (PHB), and decreased vimentin
expression. These results suggest that berberine can suppress cell growth and reduce cell survival by arresting the cell-cycle and by inducing apoptosis of HCT-8 cells.

9. Berberine: A Potential Multipotent Natural Product to Combat Alzheimer’s Disease
Hong-Fang Ji et al 2011 reported that with the accelerated aging of human society Alzheimer’s disease (AD) has become one of the most threatening diseases in the elderly. However, there is no efficient therapeutic agent to combat AD. Berberine is a natural isoquinoline alkaloid that possesses a wide range of pharmacological effects. In the present paper, we review the multiple activities of berberine, including antioxidant, acetylcholinesterase and but cholinesterase inhibitory, monoamine oxidase inhibitory, amyloid-b peptide level-reducing and cholesterol-lowering activities, which suggest that berberine may act as a promising multi potent agent to combat AD. Therefore, it is suggested that berberine is a potential multi potent agent to combat AD.

Papaya mitra mazumder et al Various pharmacognostic parameters including macroscopy, microscopy, chemo microscopy and behaviour of powdered drug on treatment with different chemical reagents were studied on the stems of Berberis aristata DC. (Family Berberidaceae). Phytochemical screening of the plant part with various solvents revealed the presence of phenolic compounds, tannins, flavonoids, phytosterols, saponins and glycosides in it. The current study was therefore carried out to provide requisite pharmacognostic details. The study might be useful to supplement information in regard to its identification parameters assumed significantly in the way of acceptability of herbal drugs in the present scenario lacking regulatory laws to control quality of herbal drugs.

11. Berberine: metabolic and cardiovascular effects in preclinical and clinical trials
Arrigo FG Cicero et al 2009, Berberine is a plant alkaloid with numerous biological activities. A large body of preclinical in vitro and in vivo studies support different pharmacological actions of berberine that could be potentially useful in the management of metabolic diseases associated with high cardiovascular disease risk, such as mixed hyperlipidemia, insulin resistance, metabolic syndrome, and type 2 diabetes. However, on the basis of the evidence cited above, we can conclude that numerous preclinical studies and some well-carried out clinical trials strongly support the potential use of berberine as a powerful insulin-sensitizing agent with relevant antihyperlipidemic effects and vascular
protective action. Further long-term randomized clinical trials have to be carried out in order to better delineate the clinical indications and the safety profile of berberine.

12. Berberine in the Treatment of Type 2 Diabetes Mellitus: A Systemic Review and Meta-Analysis, Hui Dong et al 2012, Based on the existing evidence reviewed, berberine has beneficial effects on blood glucose control in the treatment of type 2 diabetic patients and exhibits efficacy comparable with that of conventional oral hypoglycaemics. The antidyslipidemic effect of berberine need to be further confirmed. Additionally, it has no serious adverse effects except for a mild to moderate gastrointestinal discomfort. Due to the lack of high quality clinical trials, the efficacy of berberine at treating diabetes remains to be validated. This is particularly true for the effect of berberine on improving dyslipidemia in T2DM.

13. Antiproliferative activity of berberine in vitro and in vivo
Silvia Letašiovaa et al 2005 Berberine, an isoquinoline plant alkaloid acted cytotoxically in vitro on tumour cell lines B16. Its anticancer activity in vivo was studied with the transplanted B16 line in the range of doses from 1 mg/kg to 10 mg/kg. The significant reduction of tumour volume was observed on day 16 at doses of 5 and 10 mg/kg. The dose of 1 mg/kg stimulated the tumor mass, but other tested concentration, 5 and 10 mg/kg, reduced the tumour weight.

14. Activation of the aryl hydrocarbon receptor by berberine in HepG2 and H4IIE cells: Biphasic effect on CYP1A1
RadimVrzal et al 2005 studied that that berberine activates the aryl hydrocarbon receptor (AhR) in human hepatoma (HepG2) and rat hepatoma cells stably transfected with a dioxin responsive element fused to the luciferase gene (H4IIE.luc). AhR was activated by high doses of berberine (10–50 mM) after 6 and 24 h of incubation as revealed by CYP1A1 mRNA expression (HepG2) and AhR-dependent luciferase activity (H4IIE.luc). Berberine induced nuclear translocation of AhR-GFP chimera transiently transfected to Hepa1c1c7 cells. In contrast, low doses of berberine (<1 mM) and prolonged times of the treatments (48 h) failed to produce any activation of AhR in H4IIE.luc cell line. HPLC analysis ruled out the hypothesis that the loss of berberine capacity to activate AhR in H4IIE.luc cells is due to metabolic inactivation of the alkaloid. We demonstrate that berberine is a potent inhibitor (IC50 = 2.5 mM) of CYP1A1 catalytic activity (EROD) in HepG2 cell culture and in recombinant CYP1A1 protein. Collectively, our results imply that while berberine activates
the Ah receptor, it is accompanied by inactivation of the catalytic activity of CYP1A1 and occurs at concentrations that exceed those predicted to occur in vivo. Given these data, it appears that activation of the AhR pathway by berberine has a low toxicological potential.

15. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins

Weijiakong et al 2004 reported that berberine a compound isolated from Chinese herb, as a new cholesterol-lowering drug. Oral administration of BBR in 32 hypercholesterolemic patients for 3 months reduced serum cholesterol by 29%, triglycerides by 35% and LDL cholesterol by 25%. Treatment of hyperlipidemic hamsters with BBR reduced serum cholesterol by 40% and LDL-cholesterol by 42% with a 3.5- fold increase in hepatic LDLR mRNA and 2.6- fold increase in hepatic LDLR protein. Using human hepatoma cells, BBR up regulates LDLR expression independent of sterol regulatory element binding proteins, but dependent on ERK activation. BBR elevates LDLR expression through a post-transcription mechanism that stabilizes the mRNA. Using a heterologous system with luciferase as a reporter, and identify the 5’proximal section of the LDLR mRNA 3’ untranslated region responsible for the regulatory effect of BBR.

16. Genomic Screening for Targets Regulated by Berberine in Breast Cancer Cells

Chun-Jie Wen et al 2013 studied the effects of berberine on cell growth, colony formation, cell cycle distribution, and whether it improved the anticancer efficiency of cisplatin and doxorubicin in human breast cancer estrogen receptor positive (ER+) MCF-7 cells and estrogen receptor negative (ER-) MDA-MB-231 cells. The mechanisms of action of berberine, we performed genome-wide expression profiling of berberine-treated cells using cDNA microarrays. This revealed that there were 3,397 and 2,706 genes regulated by berberine in MCF-7 and MDA-MB-231 cells, respectively. Fine oncology (GO) analysis identified that many of the target genes were involved in regulation of the cell cycle, cell migration, apoptosis, and drug responses. To confirm the microarray data, qPCR analysis was conducted for 10 selected genes based on previously reported associations with breast cancer and GO analysis. In conclusion, berberine exhibits inhibitory effects on breast cancer cells proliferation, which is likely mediated by alteration of gene expression profiles.
17. Effect of Berberine on Depression- and Anxiety-Like Behaviours and Activation of the Noradrenergic System Induced by Development of Morphine Dependence in Rats

Bombi Lee et al 2012, studied berberine (BER) administration could attenuate depression- and anxiety-like behaviours and increase corticotrophin-releasing factor (CRF) and tyrosine hydroxylase (TH) expression following chronic morphine withdrawal in rats. Male rats were exposed to chronic, intermittent, escalating morphine (10~50 mg/kg) for 10 days. After the last morphine injection, depression- and anxiety-like behaviour associated with morphine discontinuation persisted for at least three days during withdrawal without any change in ambulatory activity. Daily BER administration significantly decreased immobility in the forced swimming test and increased open-arm exploration in the elevated plus maze test. BER administration also significantly blocked the increase in hypothalamic CRF expression and TH expression in the locus cerulean (LC) and the decrease in hippocampal brain-derived neurotrophic factor (BDNF) mRNA expression. Taken together, these findings demonstrated that BER administration significantly reduced morphine withdrawal-associated behaviours following discontinuation of repeated morphine administration in rats, possibly through modulation of hypothalamic CRF and the central noradrenergic system. BER may be a useful agent for treating or alleviating complex withdrawal symptoms and preventing morphine use relapses.

18. Berberine induces cell cycle arrest and apoptosis in human gastric carcinoma SNU-5 cell line,

Jing-Pin Lin et al 2006 The in vitro cytotoxic techniques were complemented by cell cycle analysis and determination of sub-G1 for apoptosis in human gastric carcinoma SNU-5 cells. Percentage of viable cells, cell cycle, and sub-G1 group (apoptosis) were examined and determined by the flow cytometric methods. The associated proteins for cell cycle arrest and apoptosis were examined by Western blotting. Berberine induces p53 expression and leads to the decrease of the mitochondrial membrane potential, Cytochrome C release and activation of caspase-3 for the induction of apoptosis.

19. Effect of berberine on pentylentetrazol-induced seizures in rats

Hamid Reza Sadeghnia et al 2011 studied that Intraperitoneal administration of lower doses of berberine (100 and 200 mg/kg) had no significant effects on minimal clonic seizures (MCS) and generalized tonic-clonic seizures (GTCS) latencies, while injection of 400 mg/kg caused significant increase in both MCS and GTCS latencies (p<0.05). In this study
diazepam, (4 mg/kg) 30 min prior to PTZ, significantly increased GTCS latency. Berberine at tested doses had no protection against mortality following PTZ administration and concluded that berberine at high doses could be a useful protective agent in PTZ induced epileptic seizures in rats.

20. Antioxidant activity of berberine on benzo (A) pyrene induced experimental lung carcinogenesis in mice, Madhusudhanan N. et al 2013 Remedial active principles of plant origin have been revealed to heal many diseases without adverse side effects. Berberine shown to be very active against experimental lung carcinogenesis. It significantly improved the antioxidant enzymes and proves its role as key modulator of lipid peroxides through its antioxidant nature and these observations are inexorably suggesting that the berberine could possibly protect against B(a)P induced carcinogenesis most likely through its strong antioxidant nature. Moreover, the Histopathological investigation also proves in cytoprotective nature of the active compound.

21. Berberine Suppresses Interleukin-1β-Induced MUC5AC Gene Expression in Human Airway Epithelial Cells, Kyung Rok Kim et al 2011, IL-1β-induced expressions of MUC5AC mRNA and protein were significantly suppressed in cells pretreated with 25 μM of berberine. Levels of MAPK proteins were determined by western blot analysis after pre treatment with 25 μM berberine. Berberine suppressed phosphorylation of extracellular signal-regulated kinase (ERK) and p38 MAPK, but there was no change in the expression of JNK. Suppression of IL-1β-induced MUC5AC mRNA was also observed in cells pretreated with ERK- or p38 MAPK-specific inhibitors, suggesting that berberine suppresses IL-1β-induced expression of MUC5AC mRNA, which involves the ERK- and p38 MAPK-dependent pathways. Berberine suppresses IL-1β-induced MUC5AC gene expression in human airway epithelial cells via the ERK- and p38 MAPK-dependent pathways; therefore, berberine may be considered as a possible anti-hyper secretory agent for inflammatory airway diseases.

22. Inhibitory Effects of Berberine on the Activation and Cell Cycle Progression of Human Peripheral Lymphocytes Lihui Xuet al 2005, investigate the effect of berberine on the activation and proliferation of lymphocytes, in particular T lymphocytes. Whole peripheral blood from healthy donors was stimulated with phyto hemagglutinin (PHA) alone or phorboldibutyrate (PDB) plus ionomycin, and the expression of CD69 and CD25 on T lymphocytes was evaluated with
flow cytometry. The distribution of cell cycles and cell viability were analysed by staining with propidium iodide (PI) and 7-aminoactinomycin D (7-AAD), respectively. The results showed that 100 μmol/L and 50 μmol/L of berberine significantly inhibited CD69 expression on T cells stimulated with PDB plus ionomycin or PHA, whereas the effect of 25 μmol/L berberine was not significant.

CONCLUSION

As compare to ancient era we know that plants chemical compounds are very useful in medicinal system as modern or other traditional system of medicine. In this paper we integrate some important aspects of berberine componds. Berberine is a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids. It is found in such plants as Berberis aquifolium, Berberis vulgaris, Hydrastis canadensis (goldenseal), Xanthorrhiza simplicissima (yellowroot), Phellodendron amurense (Amur cork tree), Coptis chinensis, Tinospora cordifolia, Argemone mexicana (prickly poppy), and Eschscholzia californica (Californian poppy). Berberine is usually found in the roots, rhizomes, stems, and bark. The morphology, macroscopy, phytochemical compounds, isolation of berberine and other important aspects of berberine are already published.

Aim of this review is that all data about berberine merge in a single paper that anyone who wants to do something better for the human being and done some new research work about berberine then without consuming any time done their work. It also has other aspects that it revealed all the knowledge about berberine.

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