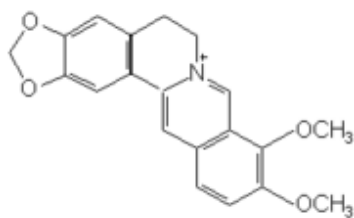


ISOQUINOLINE ALKALOIDS



Berberis vulgaris



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INTRODUCTION



Coptis occidentalis (golden thread)

Introduction to Alkaloids

Alkaloids have been the source of much human interest and fascination both in terms of scientific research and cultural usage. Often highly reactive in small amounts, their effects on the human physiology is most notable on the nervous system¹. Their use in Orthodox Medicine is prevalent (For instance the analgesic qualities of morphine) and common in Traditional Chinese Medicine. Perhaps due to restrictions, their usage is not as widespread in Western Herbal Medicine.

Alkaloids are found in 15% to 30% of all flowering plants, and are especially common in some families such as Fabaceae, Liliaceae, Solanaceae and Ranunculaceae. All species of Papaveraceae produce alkaloids. The most widely occurring of these alkaloids are *berberine* and *caffeine*. Depending on the plant species, alkaloids can occur in all parts of the plant but frequently accumulate only in particular organs e.g. in barks, roots, leaves, and fruits. In the case of *Berberis vulgaris* this is true of the bark.

Although there is still some ambiguity as to the role of Alkaloids in plants, it is suspected that rather than simply being secondary metabolites (i.e. not primary to their need for survival) they aid to protect and lengthen the survival of the plant by poisoning the taker. Most alkaloids also have a very bitter and unpleasant taste. It is also suggested that Alkaloids may serve as a storage form of nitrogen and act as a protective agent against damage of UV light.²

The effect of alkaloids on the nervous system is due to the similarity of the active nitrogen molecule which is common to neurotransmitters and influences the binding to receptor sites. The complexity of the nervous system may give alkaloids a paradoxical effect. A small dose may stimulate, and a large dose may sedate. Responses may also vary from person to person and alter pending on different circumstances³.

Alkaloids are relatively stable compounds which accumulate as the end result of different biosynthetic pathways from amino acids such as lysine, ornithine, tyrosine and tryptophan. A minority are derived from terpenoids such as *Aconite* and are given the term pseudoalkaloids. Chemically they can be differentiated from other constituents by the presence of at least one Nitrogen atom. The majority also contain Oxygen. They are generally alkaline in nature, which gives rise to the name alkaloids, although some exceptions exist such as *berberine* and *colchicine* which are acidic. They are also not usually water soluble and need organic solvents such as alcohol to be dissolved into, *Ephedrine* being an exception.

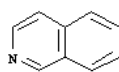
Alkaloids are a large group containing at least ten major classes. They are generally divided into Heterocyclic and Non-heterocyclic, and are grouped based on their ring structures. Most alkaloids such as the Isoquinoline alkaloids fall under the Heterocyclic alkaloids grouping.

Isoquinoline alkaloids

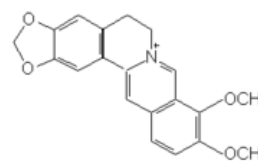
The Isoquinoline alkaloids are a large class of medicinally active alkaloids whose properties are variable. Their properties include being antispasmodic, antimicrobial, antitumour, antifungal, anti-inflammatory, cholagogue, hepatoprotective, antiviral, amoebicidal, anti-oxidant and can act as enzyme inhibitors. This class notably includes morphine and codeine. They are typically found in the Papaveraceae, Berberidaceae and Ranunculaceae families. They are derived from the amino acids phenylalanine or tyrosine. They are formed from a precursor of 3,4-dihydroxytyramine (dopamine) linked to an aldehyde or ketone⁴.

Berberine

Berberine one of the isoquinoline alkaloids, is one of the most commonly occurring of any alkaloid. It displays diverse biochemical and pharmacological actions while being relatively non-toxic to man making it widely applicable in its use. It is a major representative of the protoberberine alkaloids which are a structural class of organic cations which are characteristically yellow, have four linked benzene rings with a nitrogen atom joining two ring pairs, and are modified variously via two oxygen atoms at each end⁵.



Isoquinoline nucleus.



Berberine, C₂₀ H₁₈ N O₄.

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.

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The use of *Berberine* containing plants is prominent in both Ayurvedic and Traditional Chinese Medicine. It is also widely used in Western herbal medicine. Below is a brief list of plants which contain berberine in relatively high quantities, and their related actions. This list is significant when taking into consideration the commonalities of their action:

- *Coptis chinensis* (golden thread, Huang lian) and related species used as its substitutes have about 4-8% berberine. Commonly used in Chinese herbalism, where it is considered to be one of the 50 fundamental herbs⁶. The root is a pungent, very bitter, cooling herb that controls bacterial and viral infections, relaxes spasms, lowers fevers and stimulates the circulation. It is one of the most frequently used herbs in prescriptions for the treatment of diabetes mellitus. The root is analgesic, locally anaesthetic, anti-inflammatory, antibiotic, blood tonic, carminative, cholagogue, sedative, stomachic and vasodilator. It is particularly helpful in the treatment of diarrhoea, acute enteritis and dysentery. Externally it is used to treat various skin problems, as a mouth gargle and as an eyewash to treat conjunctivitis⁷.
- *Phellodendron amurense* (Amur cork tree, Huang Bai) Another of the 50 fundamental TCM herbs, it contains a significant 4-8% berberine⁸. It has been used to treat gastric ulcers, bacterial infections, fungal infections, and diabetes. It has also been used for immunosuppression (constituent associated with this action: *Phellodendrine*) and as a topical anti-inflammatory agent.⁹

- *Hydrastis canadensis* (Golden seal, *berberine* content 2-4.5%) which also contains *Hydrastine*, mirrors the cholaretic and antibacterial properties of berberine containing plants and is excellent for any infectious condition of the mucus membranes.¹⁰
- *Berberis aquifolium* (Oregon mountain grape) is considered similar to *B.vulgaris* (described shortly) but more gentle, a tonic for the body and particularly indicated for skin problems¹¹
- *Berberis aristate* (Tree turmeric) has been widely used in traditional Indian medicine for treatment of gastroenteritis, skin and eye infections.
- *Coccinia fenestratum* ('Columbo Tree') From Sri Lanka it is valued for its antioxidant, hypotensive, antiseptic actions and is the subject of research for diabetic use.

Barberry – *Berberis vulgaris*

Plant Part Used

Root, root bark and stem bark

Family

Berberidaceae



Active Constituents

Key constituents are Alkaloids up to 13% (protoberberines: *berberine*6%, *jatrorrhizine*, *palmatine* and *berbamine*), (bisbenzylisoquinolines: less than 5% including *oxyacanthine*), Chelidonic acid, Tannins, Wax, Resins

Actions

Cholagogue, cholaretic, mild laxative, Antibacterial (*berberine*, *palmatine*), Antimicrobial, Antiprotozoic (*berberine*), Spleen tonic, Antiemetic, Antipyretic, Anti-haemorrhagic, anti-inflammatory. The whole extract is bitter and causes relaxation of the lower bowel muscles.

Traditional uses

Some traditional uses for barberry include as blood purifier for the spring months and externally as an eye and mouth wash. The Eclectics used it in cases of jaundice (without obstruction of the bile ducts), as a digestive stimulant, for biliousness and for gallstones.

Indications

The main site of action is on the GI tract. It is a bitter and a spleen tonic. It is useful for the following conditions: cholelithiasis, cholecystitis, jaundice, portal hypertension and dyspepsia. It is also useful for infectious conditions such as Malaria, Leishmaniasis (type of protozoal infection also known as 'oriental sores') and dysentery. Clinical trials for berberine have shown its efficacy for: acute infectious diarrhoea, trachoma (used as eyedrops), adjunct in the treatment of non-insulin dependent diabetes mellitus and topical use for cutaneous leishmaniasis¹². In clinical trials berberine extracts relieved high serum concentrations of tyramine¹³ which are common in liver cirrhosis and are associated with causing cardiovascular and neuralgic complications.

Currently, the predominant clinical uses of berberine include bacterial diarrhoea, intestinal parasite infections, and ocular trachoma infections.¹⁴

Safety

Not recommended in pregnancy. In general berberine is very well tolerated both internally and externally. It is regarded as safe for long term use within recommended dosage (3-6ml per day 1:2 Fluid Extract). Death from berberine poisoning has occurred. It is known to have a strong bilirubin displacing ability

Constituents

The activity of *B.vulgaris* is thought to be due to its isoquinoline alkaloid content and in particular *berberine*. However other alkaloids present also exert their own influence and in some cases such as that of *berbamine* add to berberine's action.

Palmatine: is a hypotensive and uterine stimulant. It acts on nerve transmission to block cholinesterase and has a complex effect on the adrenal glands. As with some of the other alkaloids found in *B.vulgaris* it has anti-neoplastic properties in vitro.

Berbamine: also shares strong antibacterial qualities. It appears to increase white blood cells and platelets and has been used with some success to help with leucopenia associated from chemotherapy. It is hypertensive and depressant to the myocardium but stimulating to respiratory and skeletal muscle.

Berberine

Berberine: is considered a strong antibacterial, amoebicidal and trypanocidal and active against strains of vibrio cholera. It is anti-diarrhoeal, anticonvulsant, bile stimulating due to its bitter taste and has some uterine stimulating actions. It also stimulates blood flow to the spleen and in this way is thought to potentiate immune function and macrophage activity. *Berberine* is a known vasoconstrictor but sedative to the central nervous system. It has been reported to have direct antibacterial and anti-amoebic actions. The antibacterial properties are demonstrable even at dilutions of 1:6000¹⁵.

Pharmacokinetics

Berberine is thought to be metabolized by the liver and released as the metabolites berberrubine (M1), thalifendine (M2), demethyleneberberine (M3) and jatrorrhizine (M4) as shown after oral administration in rats. These metabolites were found in liver tissue after ½ hour and in bile after 1 hour¹⁶. In addition, *berberine* was metabolized in the liver with phase I demethylation and phase II glucuronidation¹⁷.

The amounts of metabolites were remarkably reduced in rats treated with antibiotics, although levels of *berberine* were the same. The transit time was much slower in the group treated with antibiotics. The intestinal flora did not exert significant metabolic activity against *berberine* and its metabolites, but it played a significant role in the enterohepatic circulation of *Berberine*. In this sense, the liver and intestinal bacteria participate in the metabolism and disposition of *berberine* in vivo.¹⁸

Tests have showed that *berberine* levels are at their highest in rabbits after 8 hours; oral administration of 50mg/100g was given. *Berberine* was still found to be present after 72 hours, highest levels being found in the heart, pancreas and liver. It was excreted through the stools and urine.¹⁹

Small intestine transit time in 20 healthy subjects was significantly delayed after oral administration of berberine. Thus it is thought its antidiarrhoeal ability may also be related to its ability to decrease transit time.²⁰

Pharmacodynamics

Trachoma

Although the actions of berberine alone are seen as being effectively antimicrobial (ie 0.2% berberine chloride solution) the barberry tincture is seen as being more effective. This is thought to be because of the higher concentration of berberine (0.31%) and the presence of other components.²¹ In another trial as eyedrops for the treatment of trachoma *berberine* used alone showed 84% cure, although only 50% were microbiologically cured. Trials involved children (5 months to 14 years) over a 3 month period.²²

Cholesterol

In a controlled Chinese study, it was shown that berberine, administered 500 mg twice per day for 3 months, reduced serum cholesterol by 29%, triglycerides by 35% and LDL-cholesterol by 25%. It is thought that berberine increases the production of a receptor protein in the liver which binds the LDL-cholesterol, preparing it for elimination²³.

Diabetes mellitus

Oral doses (0.3-0.5gms tds) were administered for 1-3 months with a therapeutic diet for one month. This resulted in the disappearance of major symptoms. Patients had less thirst, consumed less water and urinated less. General strength was improved, blood pressure normalized and blood lipids decreased. Fasting sugar levels were controlled in 60% of the cases. Further tests in animals suggested that the mechanism of action was by promoting regeneration and functional recovery of pancreatic β -cells²⁴. It is also thought that berberine inhibits sugars from being absorbed from the intestine²⁵.

Collaboration between Australia, China and Korea with trials on animal models of diabetes, show that berberine acts in part by activating an enzyme in muscles and liver that is involved in improving sensitivity of the tissue to insulin which then helped lower blood sugar levels. Additionally in this trial it was found that berberine may help reduce body weight²⁶.

Immune system

Berberine also shows cytotoxic effects against certain types of tumour cells and inhibitive action on tumour formation. *Berberine* has been shown to complex with DNA and is being used as a specific stain for mast cells because of its specificity of binding with heparin. It has also been shown that *berberine* exhibits the ability to induce apoptosis in promyelocytic leukemia HL-60 and 3T3 fibroblast cells²⁷. Another trial with berberine on Growth of human colon cancer cells, has shown its inhibiting effect on blocking two enzymes needed for their growth; N-acetyltransferase (NAT) and the cyclooxygenase-2 (COX-2) enzyme²⁸.

A Japanese patent published in 1995 discusses the use of berberine as an immunosuppressant specifically for autoimmune diseases such as rheumatism and also for treatment of allergies and to prevent rejection of isografts. It was found that berberine inhibits antibody production by B cells, suppresses humoral immunity and has no effect on propagation of T cells.

Cardiovascular system

Berberine can affect the timing and force of contraction of the heart and is known for its cardiostimulatory ability²⁹. In vitro studies indicate that *berberine* inhibits voltage-dependent and ATP-sensitive potassium channels, although mechanisms involved in *berberine's* anti arrhythmic activities are still unclear. *Berberine* also shows inhibition of platelet aggregation and adhesiveness as well as decreasing thromboxane B2 levels³⁰.

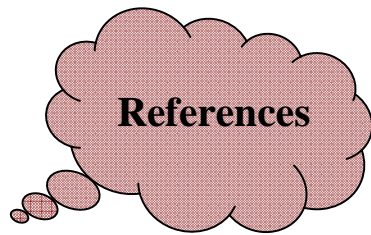
Conclusion

Based on the activities of *Berberine* many applicable uses may be seen, particularly in its use as an anti-bactericidal. It may be applied safely internally (malaria, dysentery, Giardia and a broad range of fungal infections which include Candida) and externally (Eye infections and most likely other external fungal infections). As well as its spleen stimulating activity, *Berberine* also inhibits bacteria from attaching to human cells making it useful in preventing infection.³¹

Another use which can be inferred both from herbs which contain *berberine* and information from trials, are in its use as an aid for diabetes. The rejuvenating effects on pancreatic cells are particularly positive. It may also have uses as an adjunct treatment for some heart related conditions due to the cholesterol lowering activities, platelet aggregation inhibition and cardiostimulatory effects, although this warrants further research as its primary mechanisms are not completely understood.

Useful in the treatment of some cancer cases as well as those who may be pre-disposed to cancer it is seen to inhibit tumour growth and retard development of various types of cancer by varied mechanisms³². Due to its bitterness it is also a useful cholagogue, which will have beneficial effects on the Gastro Intestinal tract due to the gentle laxative effects of bile.

Berberine has been the source of much research. It is a therapeutic constituent which is well tolerated in a range situations and age groups making it a useful and relatively safe constituent.



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