

Berberine

Old Alkaloid with wide spectrum of pharmacological activities with new anti - diabetics action

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ABSTRACT

Berberine is an isoquinoline alkaloid, present in roots and stem-bark of Berberis species. Berberine based formulations, are widely used in 3000 years old traditional systems of medicine including, Ayurveda and Traditional Chinese Medicine. Berberine has demonstrated wide range of pharmacological activities including; antihypertensive, anti-inflammatory, antioxidant, antidepressant, anticancer, anti-diarrhoeal, cholagogue, hepatoprotective and above all, antimicrobial. Recent studies, have thrown light on antidiabetic and hypolipidemic activities of the alkaloid. Berberine has been tested clinically in the treatment of oriental sore, diarrhea, trachoma diabetes mellitus type-2, hypercholesterolemia, and congestive cardiac failure.

Keywords : Berberine, pharmacology, isoquinoline alkaloid, trachoma, Diabetes mellitus-2.

Introduction :

Berberine, an isoquinoline alkaloid of the proberberine type and found in array of plants, has been used in Indian and Chinese medicine for many decades. It is present in *Hydrastis Canadensis* (goldenseal), *Coptis chinensis* (golden thread) *Berberis aquifolium* (the Oregon grape) *Berberis vulgaris* (barberry) and *Berberis aristata* (tree turmeric). However, in the last two decades a number of studies have clearly demonstrated beneficial metabolic effects including improved insulin resistance, visceral adiposity and arterogenic dyslipidemia.

Other uses are :

- (1) Anti-Proliferative And Anti-Migratory Activity
- (2) Antimicrobial Activity
- (3) Hepatoprotective Activity
- (4) Anti-Diarrheal Activity
- (5) Cholagogue
- (6) Antihypertensive Activity
- (7) Alpha 2 Adrenoceptor Antagonist Activity
- (8) Anti-Arrhythmic Activity
- (9) Antiplatelet Activity

- (10) Hypolipidemic Activity
- (11) Anti-Inflammatory Activity
- (12) Antidepressant Activity
- (13) Reno Protective
- (14) Antioxidant Activity
- (15) Trachoma
- (16) Congestive Heart Failure
- (17) Hypercholesterolemia
- (18) Type 2 Diabetes Mellitus

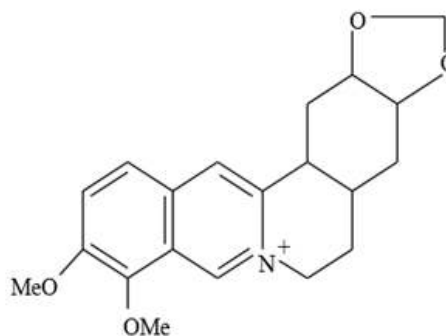


Fig-1: Chemical structure of berberine

Mechanism of Action

Berberine has been found to act on glucose metabolism through several mechanisms which decreases the glycosylated haemoglobin (HbA1C) fasting and post prandial blood sugar :

- Mimicking insulin action causing increase in insulin receptor expression.
- Improving insulin action by activating AMPK (5 AMP- activated protein kinase) intracellularly

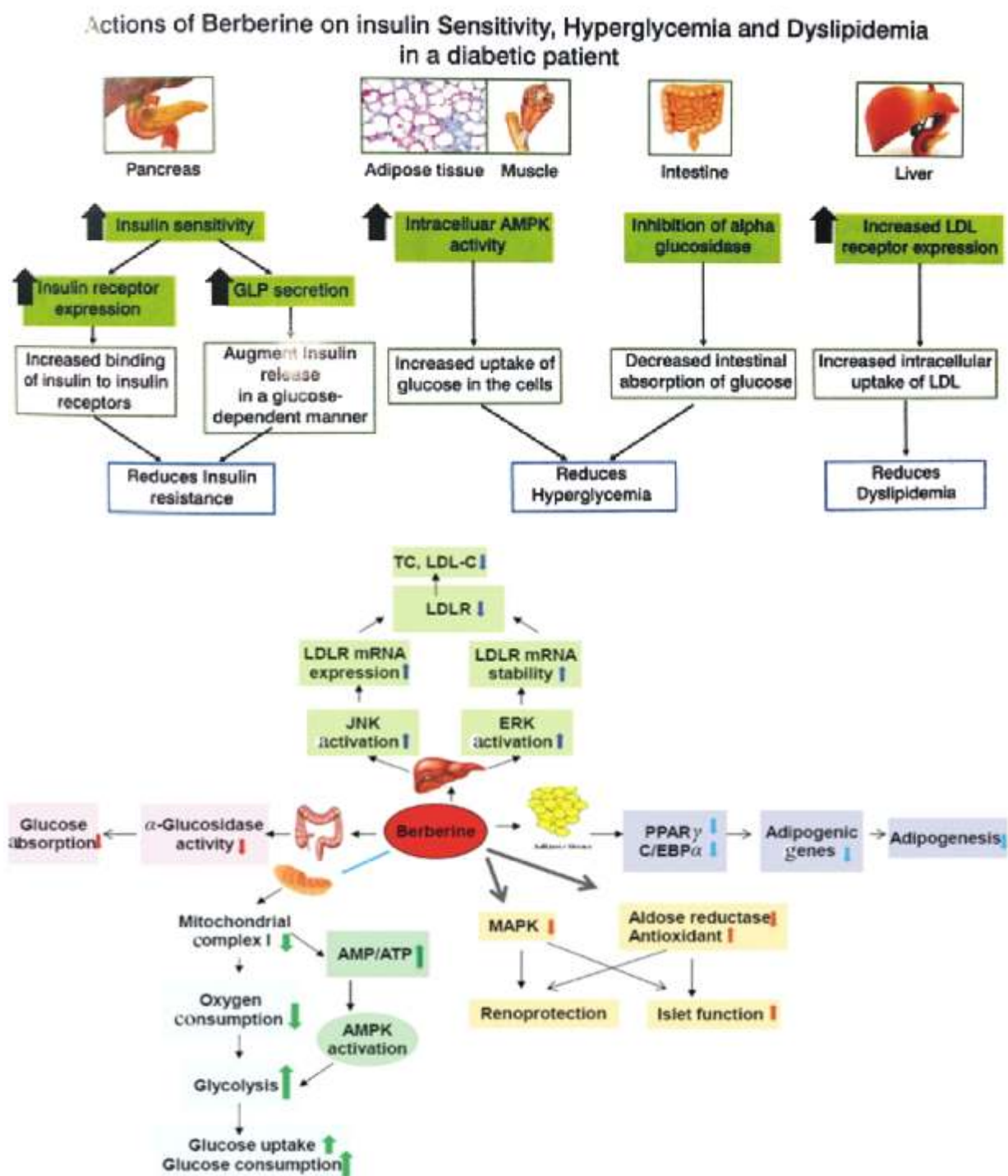
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- and enhances glucose uptake by upmodulation of GLUT-4
- Reducing insulin resistance through protein kinase C-dependent up-regulation of insulin receptor expression

- Inducing glycolysis
- Promoting GLP-1 secretion and modulating its release
- Inhibition of DPP-4



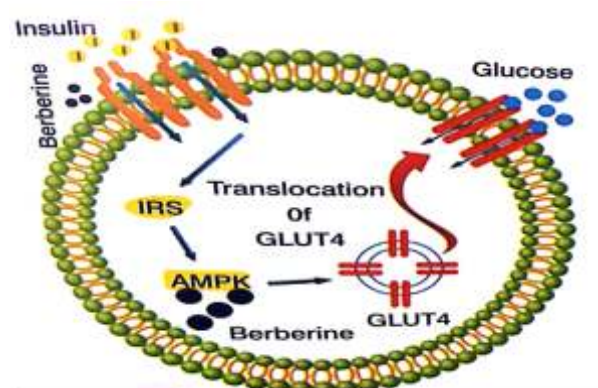
Mechanism of berberine in regulation of metabolism : (1) Berberine enhances glucose uptake through induction of glycolysis, which is due to inhibition of aerobic respiratory. AMPK activation is a consequence of inhibition of mitochondrial electron transport chain complex I; (2) Berberine is able to suppress adipogenesis through inhibition of PPAR and C/EBP function; (3) Berberine decreases intestinal glucose absorption by inhibition of α -glucosidase; (4) Berberine alleviates diabetic nephropathy and improves islet function via its antioxidant, aldose reductase and MAPK inhibitory activities; (5) Berberine upregulates LDL receptor (LDLR) expression through increasing LDLR mRNA, which is related to activation of ERK and JNK pathways

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- Inducing glycolysis
- Promoting GLP-1 secretion and modulating its release
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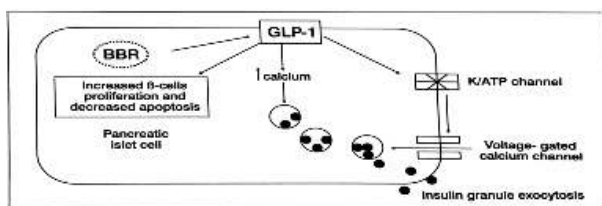
AMP-Activated Protein Kinase

The enzyme 5' adenosine monophosphate-activated protein kinase (AMPK) plays a role in cellular energy homeostasis. AMPK is expressed in a number of tissues, including the liver, brain, and skeletal muscle. AMPK acts as a “metabolic master switch” that regulates several intracellular systems, including the cellular uptake of glucose, the beta-oxidation of fatty acids, and the biogenesis of glucose transporter 4 (GLUT4). The net effect of AMPK activation is stimulation of hepatic fatty acid oxidation and ketogenesis; inhibition of cholesterol synthesis, lipogenesis, and triglyceride synthesis; inhibition of adipocyte lipolysis and lipogenesis; stimulation of skeletal muscle fatty acid oxidation and muscle glucose uptake; and modulation of insulin secretion by pancreatic beta-cells.



Incretins :

Incretins are a group of gastrointestinal hormones that cause a short-term increase in the amount of insulin released from the beta cells of the islets of Langerhans after eating, which anticipates the postprandial increase in blood glucose. They also slow the rate of absorption of nutrients into the blood stream by reducing gastric emptying and may directly reduce food intake. In addition, they inhibit glucagon release from the alpha cells of the islets of Langerhans. There are 2 main incretins : GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide). Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). Several approved drugs act on incretins. Exenatide (Byetta) is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster with biological properties similar to GLP-1. Liraglutide (Victoza) is a long-acting GLP-1 analog. Januvia (Sitagliptin) and Onglyza (Saxagliptin) are DPP-4 inhibitors.



DOSES :

IN TYPE II diabetics in addition to metformin 500 mg twice a day decreases HbA1c by 50% in patients as compared to metformin alone . maximum dose tolerated is 1.5 gms /day

Adverse effects

Berberine is **POSSIBLY SAFE** for most adults for short-term use when taken by mouth or applied to the skin.

Special Precautions & Warnings:

Children : It's **UNSAFE** to give berberine to newborns. It can cause kernicterus, a rare type of brain damage that can occur in newborns who have severe jaundice. Jaundice is yellowing of the skin caused by too much bilirubin in the blood. Bilirubin is a chemical that is produced when the old red cells break down. It is normally removed by the liver. Berberine may keep the liver from removing bilirubin fast enough.

Pregnancy and breast-feeding : It's **UNSAFE** to take berberine by mouth if you are pregnant. Researchers believe berberine can cross the placenta and might cause harm to the fetus. Kernicterus, a type of brain damage, has developed in newborn infants exposed to berberine.

It's also **UNSAFE** to take berberine if you are breast-feeding. Berberine can be transferred to the infant through breast milk, and it might cause harm.

Diabetes : Berberine can lower blood sugar. Theoretically, berberine may cause blood sugar to become too low if taken by diabetics who are controlling their blood sugar with insulin or medications. Use with caution in people with diabetes.

High bilirubin levels in the blood in infants : Bilirubin is a chemical that is produced when the old

red blood cells break down. It is normally removed by the liver. Berberine may keep the liver from removing bilirubin fast enough. This can cause brain problems, especially in infants with high levels of bilirubin in the blood. Avoid using.

Low blood pressure : Berberine might lower blood pressure. Use with caution in people with low blood pressure.

Transient gastrointestinal adverse effects with berberine were fairly common and may be related to its antimicrobial action. Berberine may be particularly useful in cases involving both type 2 diabetes and infection. Berberine should be avoided in pregnancy.

Conclusion :

Berberine acts through several mechanisms, including mimicking insulin; improving insulin action by activating AMPK; reducing insulin resistance through protein kinase C-dependent up-regulation of insulin receptor expression; inducing glycolysis; and on incretins by promoting GLP-1 secretion and modulating its release, and by inhibiting DPP-4 .additionally it shows significant effects in lipid control. There is no episode of hypoglycemia noticed in clinical trials.

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