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BERBERINE A NOVEL ANTI-DIABETIC DRUG

Abhimanyu sharma*

Amla Batra

Plant tissue culture and Biotechnology lab

Department of Botany, University of Rajasthan, Jaipur.

E.mail id:- abhsbiotech87@gmail.com

ABSRACT

Diabetes Mellitus rapidly creating a serious threat to our mankind all around the globe, So, curing of diabetes mellitus is the most essential requirement for our generation. Existing treatment options are costly and also some has side effects with limited palliative effects is the crucial requirement for human survival, due to all these drawbacks scientists searching's new medicinal or suitable prophylactic treatments. In this they are suggesting to use plant based medicinal products because of their low cost and no side effects. There are many anti- diabetic plants all of them Tinospora cordifolia are mainly using because of its fast growing propagative quality and it also contains a high quantity of Berberine. Berberine is an isoquinolene alkaloid which has significant benefit for treating diabetes and it's also having many other medicinal properties which are still exploits by many researchers. This article has been shown many medicinal properties of Beberine mainly emphasing on Diabetes Mellitus.

Keywords Diabetes Mellitus, Anti- diabetic, medicinal plants, isoquinolene alkaloid, Tinospora cordifolia, Berberine.

INTRODUCTION

Diabetes mellitus is a group of metabolic disorder in which individual has high blood glucose level either beta cell do not produce insulin in appropriate quantity or cell do not respond to the insulin (may be receptor are not effective or mutated) by these factor individual/ patient body shows some symptoms mainly polyuria (frequent urination), polyphagia (increased hunger), polydipsia (increased thirst). There are three types of diabetes-

Type 1 diabetes- This is also called insulin dependent diabetes mellitus. In this type of diabetes beta cells fail to synthesize and secrete insulin. So for treatment individual takes insulin directly

Type 2 diabetes- This is also called a non insulin independent diabetes mellitus. In this type of diabetes insulin is synthesize in appropriate quantity but cells are failure to use it.

Gestational diabetes- Some women during pregnancy has high blood glucose level, thus they show a specific type of diabetes, this is called gestational diabetes.

In some centuries countries mainly in Europe, African and in Asian herbs are classified as drugs for a treatment of many diseases. In this series many medicinal plants have been using for cure diabetes viz- Tinospora cordifolia t., Caseria esculanta roxb. , Anacardium eccidentale l., etc. these all are being studied and validated for their hypoglycemic properties using diabetic animal models. In all these plants Tinospora cordifolia has highest anti diabetic potential because of its rapidly in vivo propagative property and it's also having a high quantity of secondary metabolites. Tinospora cordifolia (Willd.) Miers Ex. Hook and Thoms is a menispermeaceae family plant, plant is a deciduous climbing shrub. It is found throughout tropical part of India. Plant contains several secondary metabolites through which plant have immense medicinal properties viz- anti diabetic, anti inflammatory, anti- leprotic, anti- spasmodic, anti- allergic, anti - stress, anti – malarial, anti- neoplastic hepatoprotective and immunomodulatory activities. Besides of all activities plant is manly using for its hypoglycemic property because plant has a high quantity of berberine. Berberine is a quaternary ammonium salt. It is a yellow colored plant alkaloid, which is why earlier time it was used to dye wool, leather and wood. Wool is still dyed with berberine I northern India. Under ultraviolet light, berberine shows a strong yellow fluorescence because of this character it is used in histology for staining heparin in mast cells. This alkaloid is present in root, root bark, stem bark and nodules in the plant body of many plants.

Uses of Berberine

Traditional use

As a traditional medicine or dietary supplement, berberine has shown some activity against fungal infections, Candida albicans, yeast, parasites, and bacterial/viral infections.[2][3] Berberine seems to exert synergistic effects with fluconazole even in drug-resistant C. albicans infections.[4]

Some research has been undertaken into possible use against MRSA infection.[5]

Berberine is considered antibiotic.[6][7] When applied in vitro and in combination with methoxyhydnocarpin, an inhibitor of multidrug resistance pumps, berberine inhibits growth of Staphylococcus aureus[8] and Microcystis aeruginosa,[9] a toxic cyanobacterium.

Berberine is a component of some eye drop formulations. There is some evidence it is useful in the treatment of trachoma,[10] and it has been a standard treatment for leishmaniasis.[11]

Berberine prevents and suppresses proinflammatory cytokines, E-selectin,[12] and genes, and increases adiponectin expression[16] which partly explains its versatile health effects. Berberine is a nucleic acid-binding isoquinolone alkaloid with wide potential therapeutic properties.[13]

Anti Microbial

Berberine has significant antimicrobial activity against variety of organism including bacteria, viruses, fungi, albicans, yeast, parasites, protozons, helminthes and chlamyda.

Anti-biotic

Berebrine is also is a antibiotic, when applied in-vitro and in combination with methoxy hydnocarpin, an inhibitor of multidry resistance pump. Instead of this bererine also inhibits growth of Staphlococcus aureus and Microcysists aeruginosa a toxic cyanobacterium.

Diabetes mellitus

Berberine has been tested and used successfully in experimental[14][15] and human diabetes mellitus.[16][17][18][19].Berberine has been shown to lower elevated blood glucose as effectively as metformin.[20] The mechanisms of action include inhibition of aldose reductase,[21] inducing glycolysis,[23] preventinginsulin resistance[24][25] through increasing insulin receptor expression[18] and acting like incretins.[26] A new study suggested berberine may overcome insulin resistance via modulating key molecules in insulin signaling pathway, leading to increased glucose uptake in insulin-resistant cells.[27]

Berberine might exert its insulinotropic effect in isolated rat islets by up-regulating the expression of hepatocyte nuclear factor 4 alpha, which probably acts solely or together with other HNFs to modulate glucokinase activity, rendering β cells more sensitive to glucose fluctuation and to respond more effectively to glucose challenge.[28]

Berberine seems to inhibit human dipeptidyl peptidase-4 (DPP IV), as well as the prodiabetic target human protein tyrosine phosphatase 1B (h-PTP 1B), which explain at least some of its antihyperglycemic activities.[29] Berberine suppresses intestinal disaccharidases with beneficial metabolic effects in diabetic states.[30]

A recent comprehensive metabonomics method, applied to 60 type 2 diabetics, suggested administration of berberine down-regulates the high level of free fatty acids which are known to be toxic to the pancreas and cause insulin resistance. These results suggest berberine might play a pivotal role in the treatment of type 2 diabetes, concluded the authors.[24]

Berberine has been shown to boost the effects of metformin and 2,4-thiazolidinedione (THZ), and can partly replace the commercial drugs, which could lead to a reduction in toxicity and side effects of the latter.[31]

Berberine inhibits Foxo1,[32] which integrates insulin signaling with mitochondrial function. Inhibition of Foxo1 can improve hepatic metabolism during insulin resistance and the metabolic syndrome.[33]

Lipids

Berberine lowers elevated blood total cholesterol, LDL cholesterol, triglycerides and atherogenic apolipoproteins (apo B) (Apo B),[34] but the mechanism of action is distinct from statins.[35][36][37]Berberine reduces LDL cholesterol by upregulating LDLR mRNA expression posttranscriptionally while downregulating the transcription of proprotein convertase subtilisin/kexin type 9 (PCSK9), a natural inhibitor of LDL receptor (LDLR),[38] and increasing in the liver the expression of LDL receptors through extracellular signal-regulated kinase (ERK) signaling pathway,[39] while statins inhibit cholesterol synthesis in the liver by blocking HMG-CoA-reductase. This explains why berberine does not cause side effects typical to statins. Berberine and plant stanols synergistically inhibit cholesterol absorption in hamsters.[40]

Berberine seems to improve the arterial endothelial function in humans.[19][41] Berberine activates AMP-activated protein kinase (AMPK),[42] specifically extracellular signal-regulated kinases(ERK),[43] which plays a central role in glucose and lipid metabolism,[44][45] suppresses proinflammatory cytokines,[46] and reduces MMP-9 and EMMPRIN expression,[47] which are all beneficial changes for heart health.

Liver

Morevover, berberine reduces hepatic fat content in the rats of nonalcoholic fatty liver disease.[48] Berberine also prevents proliferation of hepatic stellate cells (HSCs), which are central for the development of fibrosis during liver injury.[32]

Congestive heart failure

Experimental[49][50][51] and clinical studies[52][53] suggest berberine may be useful for patients with severe congestive heart failure.[54]

Transplants

According to a Chinese report, combined use of berberine with ciclosporin A (CsA) could markedly increase the blood concentration of CsA and reduce the dosage of CsA required, save the cost for medical service, and shows no obvious adverse reaction in heart-transplant recipients.[55]

Cancer

Berberine has drawn extensive attention towards its antineoplastic effects.[56][57] It seems to suppress the growth of a wide variety of tumor cells, including breast cancer,[58] leukemia, melanoma,[59] epidermoid carcinoma, hepatoma, pancreatic cancer,[60] oral carcinoma, tongue carcinoma,[61] glioblastoma, prostate carcinoma and gastric carcinoma.[62][63] Animal studies have shown that berberine can suppress chemical-induced carcinogenesis, clastogenesis,[64] tumor promotion, tumor invasion,[65][66][67][68][69] prostate cancer,[70][71][72][73] neuroblastoma,[74][75] andleukemia.[41][76]

It is a radiosensitizer of tumor cells, but not of normal cells. How berberine mediates these effects is not fully understood, but its ability to inhibit angiogenesis and to modulate Mcl-1, Bcl-xL, cyclooxygenase (COX)-2, MDR, tumor necrosis factor (TNF)- and IL-6, iNOS, IL-12, intercellular adhesion molecule-1 and ELAM-1 expression, MCP-1 and CINC-1, cyclin D1,[77] activator protein (AP-1), HIF-1, PPAR-, and topoisomerase II has been shown. By using yeast mutants, berberine was found to bind and inhibit stress-induced mitogen-activated protein kinase kinase activation. Because apoptotic, carcinogenic, and inflammatory effects and various gene products (such as TNF-α, IL-6, COX-2, adhesion molecules, cyclin D1, and MDR) modulated by berberine are regulated by the transcription factor nuclear factor- B (NF- B), it is postulated this pathway plays a major role in the action of berberine.[78] Berberine suppressed NF-κB activation induced by various inflammatory agents and carcinogens. This alkaloid also suppressed constitutive NF-κB activation found in certain tumor cells. It seems to protect against side effects of radiation therapy in lung cancer.[79]

Berberine, 300 mg three times a day orally, also seems to inhibit complication of abdominal or pelvic radiation, called radiation-induced acute intestinal symptoms.[80] The studies suggest its use in clinical development may be more as a cytostatic agent than a cytotoxic compound.

Mental health

Berberine seems to act as an herbal antidepressant and a neuroprotector against neurodegenerative disorders.[81][82][83][84] Berberine inhibits prolyl oligopeptidase (POP) in a dose-dependent manner. Berberine is also known to bind to sigma receptors like many synthetic antidepressant drugs. As berberine is a natural compound that has been safely administered to humans, preliminary results suggest the initiation of clinical trials in patients with depression, bipolar affective disorder, schizophrenia, or related diseases in which cognitive capabilities are affected, with either the extract or pure berberine. New experimental results suggest berberine may have a potential for inhibition and prevention of Alzheimer's disease (AD), mainly through both cholinesterase (ChEs) inhibitory and β-amyloids pathways,[85][86] and additionally through antioxidant capacities.[87]

Other studies have shown berberine to increase noradrenaline and serotonin levels in the brain (rats) while inhibiting dopaminergic activity.[88][89] The half-life of berberine in vivo seems to be three to four hours, thus suggesting administration three times a day if steady levels are to be achieved.[90]

Berberine seems to be able to antagonize orexin receptors, which may partly explain its metabolic, anti-Alzheimer and neurotransmitter modulating properties. [1]

Berberine may also act in a manner comparable to tianeptine by increasing the number of serotonin transporters available in the brain, enhacing the reuptake of serotonin.[91]

Intestinal disorders

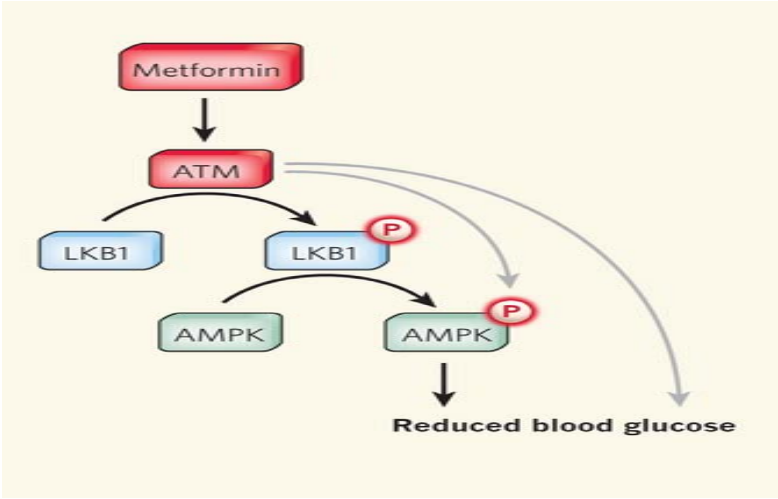
Berberine can ameliorate proinflammatory cytokines-induced intestinal epithelial tight junction damage in vitro, and berberine may be one of the targeted therapeutic agents that can restore barrier function in intestinal disease states.[92][93]

HIV

A new study identified a key cellular mechanism underlying the protective effect of berberine on HIV PI-induced inflammatory response in macrophages. Modulation of the endoplasmic reticulumstress response represents a potential therapeutic target for various inflammatory diseases and metabolic syndromes, including HIV PI-associated atherosclerosis. The report shows the potential application of berberine as a complementary therapeutic agent for HIV infection.[94]

Mechanism of berberine

Bereberine has highest anti- diabetic property because its activated AMPK (AMP- activated protein kinase), by the activation of AMPK it decreases the blood sugar and cholesterol level and it also maintain the blood pressure.. AMPK is a phlogenetically conserved serine/ theonine proein kinase, acts as anintegrator of regulatory signals monitoring systemic and cellular energy status. The growing realization that AMPK regulates the coordination of anabolic (synthesis and storage of glucose and fatty acids) and catabolic (oxidation of glucose and fatty acids) metabolic processes represents an attractive therapeutic target for intervention in many conditions of disordered energy balance. Recent evidences that pharmalogical activation of AMPK improves blood glucose homeostasis, lipid profile and blood pressure in insulin- resistant rodents. Thus, we say this protein kinase (AMPK) is a novel therapeutic target in the treatment of Type-2 diabetes.



By the signaling cascade initiated by the activation of AMPK exert effects on glucose and lipid metabolism, gene expression and protein synthesis. These effects are most important for regulating metabolic events in the liver, skeletal muscle, heart, adipose tissue and pancreas.

Some drugs which activated AMPK

Inspite of berberine there are many other therapeutic drugs which activates AMPK. Recently two major classes of drugs/ anti- diabetic drugs Biguanides and Thiazolidinediones have been using. Thus, we say by the activation of AMPK the metabolism of glucose, lipid and cholesterol will increased, by this these compounds are not accumulated in the body.

CONCLUSIONS

Berberine has definite potential as drug, since it possesses diverse pharmacological properties. Thus, we say that berberine is a novel drug for diabetes as it activates the AMPK and via activation or phosphorylation of the AMP-kinase blood sugar level is decreases. Some drugs also activates the AMPK but those has some side effects so if consume plant parts which has berberine they activate the AMPK and without any side effect blood sugar level decreases and also in very low cost.

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