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BERBERINE AND ITS PHARMACOLOGY POTENTIAL: A REVIEW

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ABSTRACT
Berberine is a naturally occurring yellow plant extract with a long history of medicinal uses in Ayurvedic and Chinese medicines. It is an alkaloid present in root, stem, bark, leaves and rhizomes of *Berberis vulgaris, Tinospora cordifolia* and many other plants. Berberine activates the enzyme called AMPK, which regulates biological activities that normalize lipid, glucose and energy imbalances. Studies have shown that berberine has various pharmacological functions such as anti-diabetic, anti-bacterial, anti-viral, anti-cancer, anti-inflammatory effects. Berberine is possibly safe to most adults for short term use and it is unsafe to newborn, infants, pregnant and nursing women and diabetic patients. The present review summarizes the pharmacology and medicinal uses of berberine.

KEYWORDS: Berberine, AMPK, berberine metabolites, pharmacology.

INTRODUCTION

Berberine is a yellow coloured bioactive compound that can be extracted from several plant species such as *Berberis vulgaris, Berberis aristata, Xanthorhiza simplicissima, Tinospora cordifolia, Argemone Mexicana, Coptis chinensis, Eschscholzia californica* etc. It belongs to a class of compound called alkaloid, meaning that it contains mainly basic nitrogen compounds.$C_{20}H_{18}NO_4$ is the molecular formula and 336.337g/mol is the molecular weight of berberine (Ye*et al.*, 2017). Plants containing alkaloids have been used as medicinal, recreational and lethal drugs for centuries.It is found in roots, rhizome, stem and bark of plant (Rajaian*et al.*, 2006). 0.04% of berberine content is present in young actively growing shoots and 1.41% in young parenchymatous roots (Srivastava*et al.*, 2015). It has a long history of use in traditional Chinese and Indian medicine, where it was used to treat various ailments. Now modern science has confirmed that it has impressive benefits for several different health problems.Alkaloids are normally alkaline and colourless but berberine is acidic in nature and identified by its bright yellow colour. Historically it has been used as a yellow dye in a number of countries (Preeti*et al.*, 2015). It has many actions in the body including anti-inflammatory, anti-tumour and broad spectrum antimicrobial against bacteria, fungus, viruses and parasites. It is powerful enough to target antibiotic resistance to have long term health benefits and it will reduces the chances of catching the flu or the viral cold due to bacterial infection. Berberine is one of the few compounds known to activate AMPK-Adenosine Monophosphate activated Protein Kinase, it is an enzyme inside the human body plays a crucial role in regulating metabolism, AMPK activation boosts fat burning in the mitochondria (Bagade*et al.*, 2017). It aids in tissue repair, maintaining a healthy heart rhythm and to control lipid and blood sugar regulations, it is normoglycemic due to AMPK activation. It blocks proprotein convertase subtilisin kexin 9 (PCSK9), which plays a key role in metabolism of lipoprotein (Cameron*et al.*, 2008). Berberine having inhibitory effects on the proliferation and reproduction of certain tumorigenic microorganisms and viruses such as hepatitis B virus and helicobacter pylori (Sun*et al.*, 2009). According to some studies berberine works by inhibiting an enzyme called PCSK9.

This leads to more LDL being removed from the blood stream (Cameron*et al*., 2008). It increases energy expenditure, limits weight gain, improves cold tolerance and enhances brown adipose tissue activity. It was shown to reduce blood pressure by competitively inhibiting vascular smooth muscle cells α_1 receptors, thereby blocking the release of the enzyme adenylyl cyclise. It promotes optimal joint health; according to 2017 berberine significantly improved joint health in rats (Wang*et al*., 2017). Berberine improves gastrointestinal and immune health by protecting mucous membrane throughout the body and it is able to fight against severe damage like that induced by heavy alcohol consumption (Wang*et al*., 2015). It also promote high bone mineral density, regular consumption of berberine improved the bone mineral density in male and female mice (Li*et al*., 2003). Several studies have suggested that berberine could help to promote optimal mental health as we age, regular consumption of berberine will increases the brain chemicals such as dopamine, serotonin and norepinephrine, all of which are necessary for healthy brain functioning and maintaining a positive mood (Kulkarni*et al*., 2008). Women with PCOS undergoing in vitro fertilization, berberine is superior to metformin at achieving more live births with fewer side effects (An*et al*., 2014). Pre-treatment with berberine significantly reduces the effect of cigarette smoke induced acute lung inflammation through its anti inflammatory activity (Lin*et al*., 2013).

CHEMICAL PROPERTIES

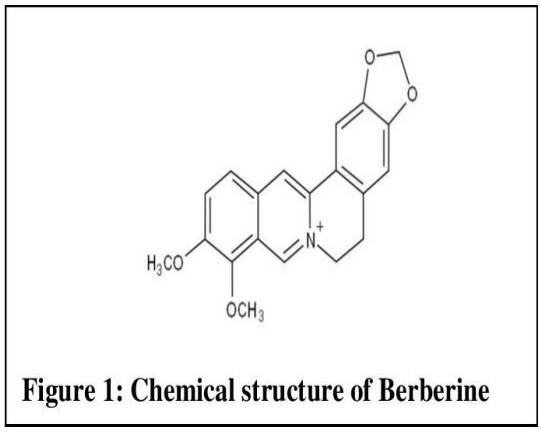

Figure 1: Chemical structure of Berberine

TRADITIONAL USES OF BERBERINE

Berberine based formulations, are widely used in traditional systems of medicine including Ayurveda and Traditional Chinese medicine and berberis species has 3000 years of history(Singh*et al*., 2010).Genus berberis comprises 12 genera, 600 species worldwide and 77 species have been reported in India in Berberidaceae family, which represents the main natural source of berberine (Chander*et al*., 2017). Berberine containing plants are used to cure inflammation, infectious disease, diabetes, constipation and other pathologies. Oldest evidence shown that barberry fruit was used as a blood purifying agent. In Ayurveda berberine containing plants are used for the treatment of infection on eye, ear, quick healing wound, antidote, scorpion sting and snake bite. Use of decoction of Indian barberry mixed with honey has also been reported for the treatment of jaundice, decoction of Indian barberry and *Emblic myrobalan*with honey can cure urinary disorders such as painful micturition (Neag*et al*., 2018).*Rasont* is a decoction of the roots, stem and bark of Indian berberis species, which have been used to cure ophthalmic disease, jaundice, enlarged liver and spleen and also for skin disease like ulcers (Rajasekaran*et al*., 2009).

PHARMACOLOGY OF BERBERINE

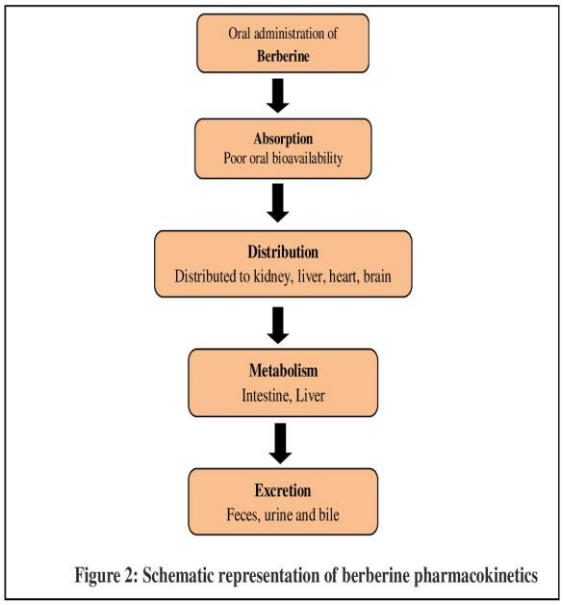

Figure 2: Schematic representation of berberine pharmacokinetics

a) ABSORPTION

Berberine has an extremely low oral bioavailability. Berberine is appears to be subject to P-Glycoprotein mediated efflux from the intestine and liver. In the intestine P-Glycoprotein is responsible for 90% reduced transportation of berberine, which ejects berberine back into the intestine (Chae*et al*., 2008). But absorption is greatly increased when taken with P-Glycoprotein inhibitors such as cyclosporine A, Verapamil (Pan*et al*., 2002).

b) DISTRIBUTION

Animal study showed that after oral administration berberine has high tissue distribution. It is quickly distributed in the liver, kidney, heart, brain, lungs, muscle, pancreas and fats (Tan*et al*., 2013) and there is no human study about the distribution of berberine (Imenshahidi*et al*., 2019).

c) METABOLISM

Both in rats and humans liver is the main place of berberine metabolism. CYP2D6 is the primary human cytochrome P450 for producing berberine's metabolites followed by CYP1A2, 3A4, 2E1 and CYP2C19 (Guo*et al*., 2017). CYP2D6 has an important role in berberine metabolism because it is responsible for 9% of the berberine metabolite berberrubine (M1) and 8% of thalifendine (M2). CYP2D6 pharmacogenetics and drug-

drug interactions should be considered in berberine administration (Imenshahidi*et al*., 2016).After undergoing demethylation in phase I,berberine metabolites of M1 and M2 conjugated with glucuronic acid and sulphuric acid and make phase II metabolites. Both M1 and M2 can be glucuronidated by UGT2B1and UGT1A1. These glucuronide metabolites are polar and easily excreted (Imenshahidi*et al*., 2019).

d) EXCRETION

There is no human study about excretion of berberine. In an animal study with rat, total recovered rate of berberine was 22.83% (Imenshahidi*et al*., 2019). Major route of excretion of berberine is fecal; the major metabolites of berberine such as thalifendine (M1), berberrubine (M2) mostly excrete through bile and urine (Imenshahidi*et al*., 2016).

BIOLOGICAL ACTIVITIES OF METABOLITES OF BERBERINE

Berberine has exhibited marked biological activities and the concentrations of its major metabolites such as thalifendine, jatrorrhizine, demethyleneberberine, berberrubine were at relatively high levels even though berberine possesses low oral bioavailability (Zuo*et al*., 2006).

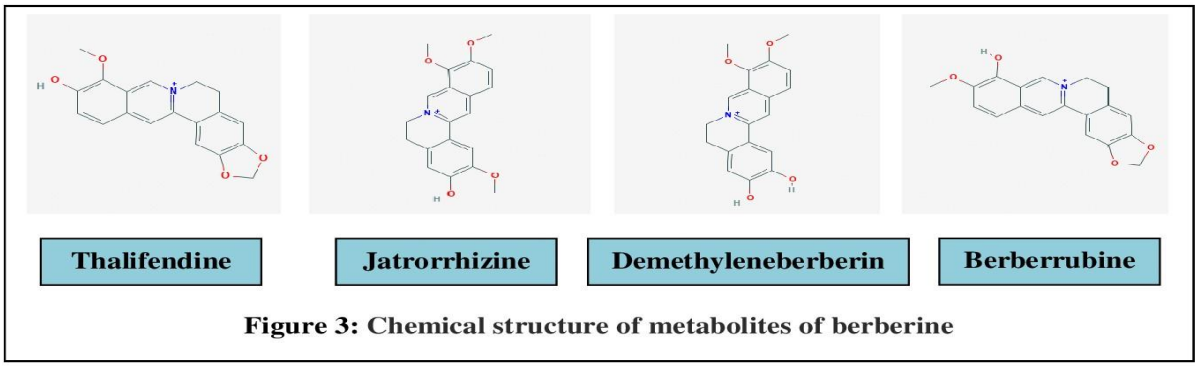

Figure 3: Chemical structure of metabolites of berberine

Metabolites of berberine are active constituents, which are representatives for the biological activities of berberine *in vivo* (Wang*et al*., 2017). Metabolites of berberine similar bioactivities, both berberine and its metabolites have hypolipidemic effects; columbamine exhibit marked potential effects on triglycerides, jatrorrhizine exhibit anti-microbial, hypolipidemic and hypoglycemic effects (Yan *etal*., 2008).

Table 1: List Of Plants Contain Berberine

Sl.No	Scientific name of plant	Common name of plant	Plant part	Reference
1.	*Argemone Mexicana*	Prickly poppy	Leaves	(More *et al*., 2017)
2.	*Berberis vulgaris*	Barberry	Root	(Imenshahidi *et al*., 2016)
3.	*Berberis aristata*	Tree turmeric	Root, stem bark	(Kattiyar *et al*., 2014)
4.	*Berberis lyceum*	Boxthorn barberry	Root	(Khan *et al*., 2016)
5.	*Berberis asiatica*	Chutro	Root	(Furrianca *et al*., 2015)
6.	*Berberis aquifolium*	Oregon grape	Root	(Neag *et al*., 2018)
7.	*Berberis floribunda*	Nepal barberry	Root	(Neag *et al*., 2018)
8.	*Berberis congestiflora*	Michay	Leaves and stem	(Neag *et al*., 2018)
9.	*Berberis croatica*	Croatian barberry	Root	(Neag *et al*., 2018)
10.	*Berberis petiolaris*	Chochar	Root	(Singh *et al*., 2015)
11.	*Berberis tinctoria*	Nilgiri barberry	Stem bark	(Deepak *et al*., 2014)
12.	*Coelocline polycarpa*	Yellow dry tree of Soudan	Bark	(Neag *et al*., 2018)
13.	*Coptis chinensis*	Chinese goldthread	Root	(Neag *et al*., 2018)
14.	*Coptis japonica*	Japanese goldthread	Rhizome	(Otani *et al*., 2005)
15.	*Eschscholzia californica*	Californian poppy	Root	(Neag *et al*., 2018)
16.	*Hydrastis Canadensis*	Goldenseal	Root	(Weber *et al*., 2003)
17.	*Mahonia aquifolium*	Oregon grape	Root	(Kostalova *et al*., 1981)
18.	*Phellodendron amurense*	Amur cork tree	Bark	(James *et al*., 2011)
19.	*Papaver dubium*	Long head poppy	Root	(Mat *et al*., 2000)
20.	*Papaver hybridum*	Poppy	Aerial root	(Neag *et al*., 2018)
21.	*Rollinia deliciosa*	Wild sugar apple	Fruit	(Chan et al.,1996)
22.	*Xanthorhiza simplicissima*	Yellow root	Root, stem	(Neag et al., 2018)
23.	*Tinospora cordifolia*	Heart leaved moonseed	Leaf, stem	(Abhinay et al., 2017)
24.	*Xylopia macrocarpa*	Jangkang	Stem bark	(Neag et al., 2018)

AMPK ACTIVATION OF BERBERINE

AMP-activated protein kinase or 5' adenosine monophosphate –activated protein kinase is an enzyme play an essential role in cellular metabolism, largely to activate glucose and fatty acid uptake and oxidation when cellular energy is low. AMPK activation results in an increase in the uptake of glucose from the blood to target organ and it inhibits the accumulation of fat by modulating down-stream signaling components like acetyl CoA corboxylase –ACC. By direct phosphorylation AMPK inhibits acetyl CoA corboxylase and it blocks the fatty acid synthesis pathways (Zhou*et al*., 2008).

The beneficial effects of berberine are attributable to its effect as an AMPK activator.

Administration of Berberine

⇩

Berberine gets inside the body and transported into the blood stream

⇩

Travel into body's cells

⇩

Inside the cell berberine binds to several different molecular targets and changes their function (Jing*et al*., 2015).

Berberine activates AMPK in a dose and time dependent manner and increases the phosphorylation of the 125-kDa precursor form of SREBP-1c and it suppresses its proteolytic processing into the mature 68-kDa form and its subsequent nuclear translocation (Jang*et al*., 2017).Berberine activates AMPK in adipocytes and muscle cells and reduces fat accumulation and improves insulin sensitivity (Lee*et al*., 2006). It inhibits mitochondrial respiratory chain complex 1 by activating AMPK (Jang*et al*., 2017).It increases AMPK activity in 3T3-L1 adipocytes and L6 myotubes and increases GLUT4 translocation in L6 cells in a phosphatidylinositol 3′ kinase independent manner and reduces lipid accumulation in 3T3-L1 adipocytes (Lee*et al*., 2006). Berberine suppresses colon epithelial proliferation and tumorigenesis through AMPK dependent inhibition of mTOR activity and AMPK independent inhibition of NF-κB (Li*et al*., 2015).

PHARMACOLOGICAL EFFECTS OF BERBERINE

❖ **CENTRAL NERVOUS SYSTEM**

➢ **Alzheimer's disease**

Alzheimer's disease is a progressive disease that destroys memory and other important mental function. Its symptom comes gradually and affects the brain and degenerative, meaning they cause slow decline. Hypertension, diabetes, dislipidemia are the risk factors play a role in the development of Alzheimer's disease. Targeting these risk factors will minimize the burden of Alzheimer's disease. Berberine is considered as a potential therapeutic approach to prevent and delay the process of Alzheimer's disease by limiting the role of these risk factors and also improving the metabolic syndrome associated with Alzheimer's disease (Cai*et al*., 2016).

➢ **Depression**

Depression is a mental health disorder characterized by depressed mood, loss of interest in daily activities causing significant impairment in daily life. Antidepressants are medication used to treat symptoms of depression, social anxiety disorder, dysthymia and other conditions. Monoamine oxidase inhibitors are the important group of antidepressants. It is an enzyme that decomposes the neurotransmitters such as serotonin, noradrenaline and dopamine in the neural tissue, which are deficient in the brain leads to depression. By inhibiting the monoamine oxidase, inhibitorsof this enzyme raise the concentration of key neurotransmitters in the brain, giving a clear improvement in the pharmacological treatment of depression. Berberine is capable to inhibit monoamine oxidase activity and alleviate the symptoms of depression (Kong*et al*., 2001).

❖ **CARDIOVASCULAR EFFECTS**

➢ **Atherosclerosis**

Atherosclerosis is a condition in which plaques are build-up in the artery walls leads do narrowing and hardening the arteries.This disease disturbs the blood flow around the body, posing the risk of serious complications. Monocyte adhesion to the endothelium is an initial stage atherosclerosis development. Berberine will reduces the number of adherent monocytes on endothelial cells and it suppresses proinflammatory cytokines induced by hyperglycaemia and involved in the development of atherosclerotic plaques (Bagade*et al*., 2017). Berberine is able to prevent HIV protease inhibitor induced atherosclerosis by inhibiting the unfolded protein response activation and the inflammatory response in macrophages (Zhou*et al*., 2008).

➢ **Heart failure**

Heart failure is also known as congestive heart failure, it happens when the heart muscle doesn't pump the blood. High blood pressure, narrowed artery in the heart can make the heart weak. Calcium plays an important role in maintaining normal blood pressure.One of the studies suggested that berberine has improved the cardiac functions by increasing the concentration of calcium in cardiac muscle cells. Berberine increases the high energy phosphate in heart failure, due to its effect on potassium channels berberine prevent ventricular fibrillation and suppressed the delay of depolarization partly due to sodium influx. And also berberine decreased plasma noradrenalin and adrenaline levels and adrenaline in

ventricular tissue and improves cardiac contractility in experimentally induced rat. Berberine stimulates the release of nitric oxide which relaxes the arteries, increases blood flow, lowers blood pressure and protects against atherosclerosis (Xia*et al*., 2015).

➢ **Hypercholesterolemia**

Hypercholesterolemia is a condition characterized by very high levels of cholesterol in the blood. Berberine has been found to lowers lipid level by different mechanisms. Oral administration of berberine at 100mg/kg/day for 4 weeks reduced blood total cholesterol by 16%, LDL-cholesterol by 20% and increased HDL-cholesterol by 9% in Kunming mice with Streptozotocin (STZ) induced diabetes. But a stronger effect was observed in male diabetic KKAy mice fed a high fat diet. Oral administration of berberine at 250mg/kg/day for 4 weeks reduced blood total cholesterol by 42%. Berberine is normally administered through diet or oral and in few studies injection was used. In some clinical studies berberine was administered in tablet form of a nutraceutical product and this product have shown a marked cholesterol lowering effect (Wang*et al*., 2018).

❖ **ENDOCRINE EFFECTS**

➢ **Polycystic ovary syndrome**

Polycystic ovary syndrome is a condition in which women produce higher amount of male hormone than normal. It affects woman's hormone level causes them to skip menstrual cycle and makes it harder for them to get pregnant. Women with PCOS having high insulin level can cause ovaries to make more androgen hormones such as testosterone. Through the activation of AMP activated protein kinase pathway berberine improves the insulin signal transduction by stimulating glucose intake (Wei*et al*., 2012). Berberine has been shown to improve ovulation in women with PCOS and also improves pregnancy rate with IVF treatment. Berberine has been shown to reduce the androgen level, testosterone and free androgen index level in women with PCOS. And Berberine also increased sex hormone binding globulin level in three months of use (An*et al*., 2014).

➢ **Obesity**

Obesity is a disorder involving excessive body fat; this condition puts people at a higher risk of health problems such as type 2 diabetes, heart disease and cancer. Berberine is one of the few compounds known to activate AMPK. Activation of AMPK boosts fat burning in the mitochondria. It increases the basal lipolysis state of triglycerides in adiposities. It can reduce the accumulation of fat in human the body. Berberine has been shown to be a potential drug to treat obesity by down regulation of adipogenesis and lipogenesis (Wang*et al*., 2017). Obesity is also caused by accumulation of TG in adipose tissue. Berberine reduces the number and size of lipid droplets in 3T3-L1 adipocytes. Berberine decreases the obesity by suppressing adipocyte differentiation (Firouzi*et al*., 2018).

➢ **Diabetes mellitus**

Diabetes mellitus is a metabolic disorder in which a person having high blood sugar level over a prolonged period. Insulin resistance and β-cell damage is the main cause of type-2 diabetes. In patient with poor β-cell function, berberine has improved insulin secretion by repairing the destructed or exhausted islets (Yin*et al*., 2012). It has beneficial effects on blood glucose control in the treatment of type 2 diabetic patients and it has no serious adverse effects except for a mild to moderate gastrointestinal discomfort (Dong*et al*., 2012).

❖ **GASTROINTESTINAL TRACT**

➢ **Liver fibrosis**

Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occur most types of chronic liver diseases. Berberine has inhibited the proliferation of rat hepatic stellate cells and induced cell cycle arrest in G1 phase; by this way berberine prevent hepatic fibrosis. Berberine can prevent experimental liver fibrosis through regulation of lipid peroxidation and anti-oxidant system (Imenshahidi*et al*., 2016).

➢ **Non-alcoholic fatty liver disease (NAFLD)**

Non-alcoholic fatty liver disease is a very common disorder where there is accumulation of excess fat in the liver of people who drink little or no alcohol. Berberine is a potential drug for NAFLD in both experimental models and clinical trials. Berberine strongly reduces the fat storage in the liver to hyperlipidemic hamsters and for mice with high fat diet (HFT) berberine reduced the hepatic steatosis and decreased 14% of liver lipid content (Liu*et al*., 2013). It has also shown to reduce liver necrosis both in non-alcoholic steatosis and in steatosis due to hepatitis C infection (Zhang*et al*., 2008).

➢ **Diarrhoea**

Berberine is known for its anti-diarrhoeal activity. Berberine decreases bacterial adherence to mucosal or epithelial surfaces. It was demonstrated that berberine is an effective and safe anti-secretary drug for diarrhoea caused by microbial enterotoxins. It reduces the epithelial permeability in the gut by reinforcing tight junctions in the CaCo2 cell line and significantly increases transepithelial electrical resistance (Chen*et al*., 2014).

❖ **ANTI-INFLAMMATORY EFFECT**

➢ **Bacterial infection**

Recent literature reports demonstrated that berberine is active against gram positive bacteria but less active against gram negative bacteria. It has also shown to inhibit Helicobacterium Pylori. It had also shown response against multidrug resistant strains of TB bacilli (Patil*et al*., 2015). Fts-Z is an essential bacterial cytoplasm cytokinesis protein. Berberine is able to target

Fts-Z protein, inhibits the assembly kinetics of Z ring and perturbs cytokinesis. It destabilizes the Fts-Z protofilaments and inhibits Fts-Z GTPase activity (Domadia*et al*., 2008).

➢ **Parasitic infection**

Berberine shows anti-parasitic effect on anaerobic protozoa such as Giardia lamblia, Trichomonas vaginalis and Entamoeba histolytica. It also showed anti-parasitic effect on dog roundworm (Taxocara canis) in cell studies (Kaneda*et al*., 1990). Berberine combined with Pyrimethamine (Malaria medication) is more effective against getting rid of infection than other combination of drug such as Pyrimethamine and Tetracycline or Pyrimethamine and cortimoxazole (Sheng*et al*., 1997).

➢ **Viral in.fection**

Berberine showed strong inhibition on the growth of H1N1 influenza A strains PR/8/34 or WS/33 in RAW 264.7 macrophages like cells, A549 human lung epithelial derived cells and murine bone marrow derived macrophages (Cecel*et al*., 2011). Berberine showed antiviral activity against herpes simplex virus, it reduced viral RNA transcription, protein synthesis and virus titers in a dose dependent manner(Song*et al*., 2014). Berberine found to be the most active compound with an EC 50 of 0.13µM against HIV-1 NL 4.3 virus in CEM-GFP cell line (Bodiwala*et al*., 2011).

SIDE EFFECTS OF BERBERINE

Berberine side effects are often overlooked because of the low berberine toxicity rating. Generally berberine has shown very low toxicity and side effects in animal studies (Mohammadzadeh*et al*., 2017). However, there are definitely some side effects of berberine to look out for. Due to the risk of bilirubin-induced brain damage berberine and berberine containing plants should be avoided from jaundice infants and pregnant women and also nursing women (Zhi*et al*., 2002). Allergic reactions have been reported after intravenous administration of berberine (Bagade*et al*., 2017). Main side effects are related to digestion, cramping, diarrhoea, flatulence, constipation and stomach pain (Yin*et al*., 2008).Mild adverse effects are such as nausea, distension, diarrhoea and constipation (Dong*et al*., 2012). High doses of berberine may cause arterial hypotension, dyspnea, flulike symptoms, cardiac damage and gastric lesions (Bagade*et al*., 2017).

CONCLUSION

Berberine is a quaternary ammonium salt from the protoberberine group of benzylisoquinoline alkaloid, which is present in number of medicinal plants that have been widely used in traditional Chinese medicine for hundreds of years. Phytochemistry literature revealed that species are rich in alkaloids, of which biologically active berberine is the major and the potential one. Modern research has shown that berberine display several pharmacological effects through various mechanisms. It is a natural drug for the clinical uses in different disease and pathological conditions such as atherosclerosis, cancer, alzheimer's disease, diabetes, PCOS, bacterial and viral infections etc. It has very low toxicity in usual doses and reveals clinical benefits without major side effects. It can be a potential source for future drug discovery and drug development.

ABBREVIATIONS

- AMPK- Adinosine Monophosphate-activated Protein Kinase
- PCSK9-Proprotein ConvertaseSubtilisin Kexin
- LDL- Low Density Lipoprotein, HDL- High Density Lipoprotein
- PCOS- Polycystic Ovarian Syndrome
- CYP2D6- Cytochrome P450 2D6
- M1 and M2- Metabolites 1 and 2
- UGT-UDP Glucuronosyl Transferaces
- ACC- Acetyl CoA Carboxylase
- SREBP- Sterol Regulatory Element Binding Protein
- GLUT- Glucose Transport type
- mTOR- mammalian Target Of Rapamycin
- NF-kB- Nuclear Factor kappa-light-chain enhancer of activated B cells.

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