Global SciTech Ocean

Current Medical and Drug Research

(Contents available at www.globalscitechocean.com)

Research article

Spectral studies and pharmacological relevance of berberine isolated from *Berberis aristata* roots

Ruchi Badoni Semwal[1,2,*], Deepak Kumar Semwal[3], Sonali Aswal[4] and Ankit Kumar[5]

[1]*Department of Chemistry, Panjab University, Sector 14, Chandigarh-160014, India*
[2]*Department of Chemistry, Pt. Lalit Mohan Sharma Govt. Postgraduate College, Rishikesh- 249201, Uttarakhand*
[3]*Department of Phytochemistry, Faculty of Biomedical Sciences, Uttarakhand Ayurved University, Harrawala, Dehradun-248001, India.*
[4]*Research and Development Centre, Faculty of Biomedical Sciences, Uttarakhand Ayurved University, Harrawala, Dehradun-248001, India.*

*Corresponding author: E-mail: ruchi_badoni26@yahoo.com; Tel: +91- 8477961080.

Article history

Received : February 08, 2018
Accepted : March 26, 2018

Keywords

Ayurvedic medicine
Diabetes
Nuclear Magnetic Resonance
Rasaut
Protoberberine alkaloids

ABSTRACT

Berberis aristata DC., commonly known as Indian barberry or Daruharidra, belongs to the Berberidaceae family. The plant root is well-known Ayurvedic medicine for diabetes, eye problems, skin disorders, and urinary tract diseases. The plant contains a variety of alkaloids including berberine, oxyberberine, berbamine, aromoline, karachine, palmatine, oxycanthine and taxilamine. The plant is reported to have hypoglycemic, antimicrobial, antipyretic, anti-inflammatory, hepatoprotective, antioxidant, anticancer and antiplatelet activities in different experimental models. In the present study, berberine was isolated in the form of its chloride salt from the roots of *B. aristata*. The molecule was characterised by a detailed spectral analysis including two-dimensional NMR studies. The molecule was also reviewed for its pharmacological relevance together with the possible mode of action.

INTRODUCTION

Berberis aristata DC. (Berberidaceae) is popularly known as Daruharidra in Ayurveda. It is an erect spiny shrub of 2-3 m tall (Fig. 1). The outside bark is yellow to brown and inside bark is deep yellow which is covered with three-branched thorns or modified leaves. The leaves are arranged in tufts of 5-8 and are approximately 5 cm long and 2 cm broad. These are deep green on the dorsal surface and light green on the ventral surface, simple with pinnate venation, leathery in texture and are toothed, with many small indentations along the margin of the leaf. The flowers are yellow, complete and hermaphroditic with an average diameter of 12.5 mm. These form a racemose inflorescence, with 11-16 flowers per raceme, arranged along a central stem. These are polysepalous (3 large and 3 small sepals) and polypetalous (6 petals). The flowers usually bloom during March-April. *B. aristata* produces bunches of succulent, acidic, edible berries of bright red colour. The berries are approximately 7 mm long, 4 mm in diameter with an approximate weight of 200 mg, and ripening during May-June (Parmar and Kaushal, 1982). The fruits are juicy and contain plenty of sugars, vitamin C and other useful nutrients. In Ayurveda, the plant is used for diabetes, wound healing, swelling, piles, pimples, boils, ulcers, sores, eye disorders, leucorrhoea, anorexia, dysentery, hepatitis, liver disorders, cough, blood purification, jaundice, obesity and fever. The roots of the plant are also used for making an alcoholic drink as well as a yellow fabric dye (Semwal et al., 2012). Rasaut is a popular Ayurvedic preparation of this plant used for eye disease, skin disorders, and indolent ulcers (Srivastava and Rawat, 2013).

Preliminary phytochemical screening of the root revealed the presence of alkaloids, flavonoids, saponins, steroids, terpenoids and tannins. The alkaloids are major constituents of the plant which include berberine, palmatine, berbamine, oxyberberine, oxycanthine, karachine, aromoline, epiberberine, dihyrokarachine, dehydrocaroline, jatrorrhizine, columbamine, taximaline, pakistanine, 1-O-methylpakistanine, pseudopalmatine and pseudoberberine (Mokhber-Dezfuli et al., 2014).

Fig. 1. *Berberis aristata* in its natural habitat

Various parts of the plant have been evaluated for a variety of pharmacological activities. The plant showed antimicrobial, CNS depressant, anticancer, immunomodulatory, hepatoprotective, anti-inflammatory, antipsoriatic, antimalarial and antidiabetic activities in various experimental models (Singh and Kakkar, 2009; Chandel et al., 2015).

Berberine (Fig. 2), a quaternary ammonium alkaloid of benzylisoquinoline class is found mainly in *Berberis aristata* and *Berberis vulgaris*. It is widely used in Asian countries as a traditional medicine to treat intestinal infections, diabetes and UTI (Liu et al., 2012). It was found to exhibit antimicrobial, antidiabetic, antiobesity, hypotensive, hypo-lipidemic, antiinflammatory and anti-carcinogenic activities (Tabeshpour et al., 2017).

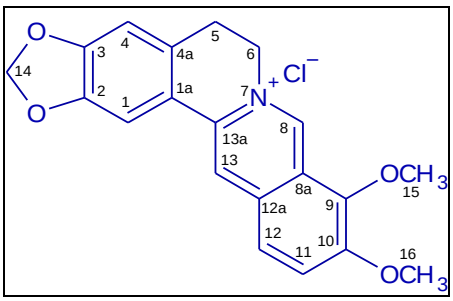
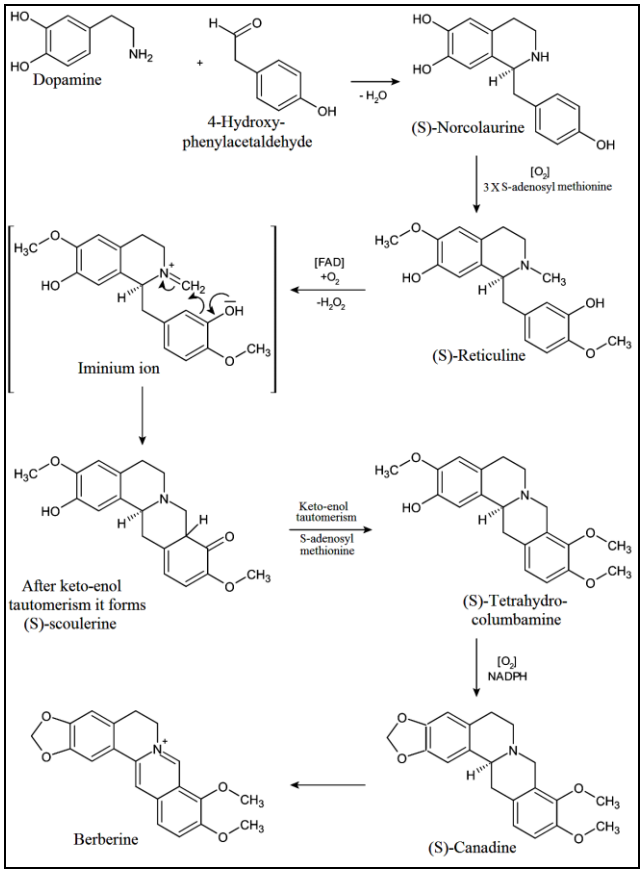


Fig. 2. Chemical structure of berberine

A biosynthesis for the berberine is depicted in Scheme 1 in which reticuline is the immediate precursor of berberine in plants (Dewick, 2009). Berberine is derived from tyrosine, and L-DOPA and 4-hydroxypyruvic acid both come from L-tyrosine. Although two tyrosine molecules are used in the biosynthetic pathway, only the phenylethylamine fragment of the tetrahydro-isoquinoline ring system is formed via DOPA, the remaining carbon atoms come from tyrosine via 4-hydroxyphenylacetaldehyde. L-DOPA loses CO_2 to form dopamine. 4-Hydroxypyruvic acid by losing CO_2 to form 4-hydroxyphenylacetaldehyde. Dopamine then reacts with 4-hydroxyphenyl-acetaldehyde to form (S)-norcolaurine which formed (S)-reticuline after oxidation and methylation by S-adenosyl methionine. Oxidation of the tertiary amine then occurs and an iminium ion is formed which convert to (S)-scoulerine after keto-enol tautomerism and after methylated by S-adenosyl methionine, it forms (S)-tetrahydro-columbamine. The (S)-canadine is then formed via an O_2^-, $NADPH^-$ and cytochrome P-450-dependent enzyme which ultimately forms berberine after oxidation. In the present work, we isolated berberine from the roots of *B. aristata* and described its structure with the help of detailed spectral analysis.



Scheme 1. Biosynthesis of berberine

MATERIALS AND METHODS

General

NMR spectra were scanned on a Bruker Avance, auto sampler (400 MHz for ^1H & 100 MHz for ^{13}C in MeOH, with TMS as an internal standard. MS was obtained on a LC-MS, Finnigan Mat, LCQ (n = 9 with APCI/ESI Probe). Separation was done through silica gel column (Merck, India, 60–120 mesh); TLC used was aluminium-backed, precoated with silica gel (Merck, India). The spraying reagent 7% H_2SO_4 followed by heating was used to visualising the spots.

Plant material

Fresh roots of *B. aristata* were collected Village Chaka, Near Chandravadani Temple, Uttarakhand (India), during September 2012. The plant material was authenticated by Botany Department, Panjab

University, Chandigarh and a voucher specimen (17919) was deposited in the departmental herbarium.

Extraction and isolation

Shade-dried and powder roots (500 g) were extracted thrice with methanol (500 mL) for 12 h at room temperature. The solvent was evaporated up to dryness in a rota-evaporator with the maintained temperature at 40 °C to yield black-brown extract (50 g). The extract was pretreated with silica gel of equal ratio and applied on the top of a silica gel packed column. The column was first eluted with chloroform followed by increasing volume of methanol by 5%. An elution of chloroform: methanol (9:1) furnished a methanol soluble yellow powder.

Spectral analysis

The NMR and MS studies were carried out at the National Institute of Pharmaceutical Education and Research, Mohali, Punjab (India). The deuterated methanol (CD_3OD) was used as a solvent for NMR spectral analysis. The NMR and mass spectra are given in Fig. 3-6.

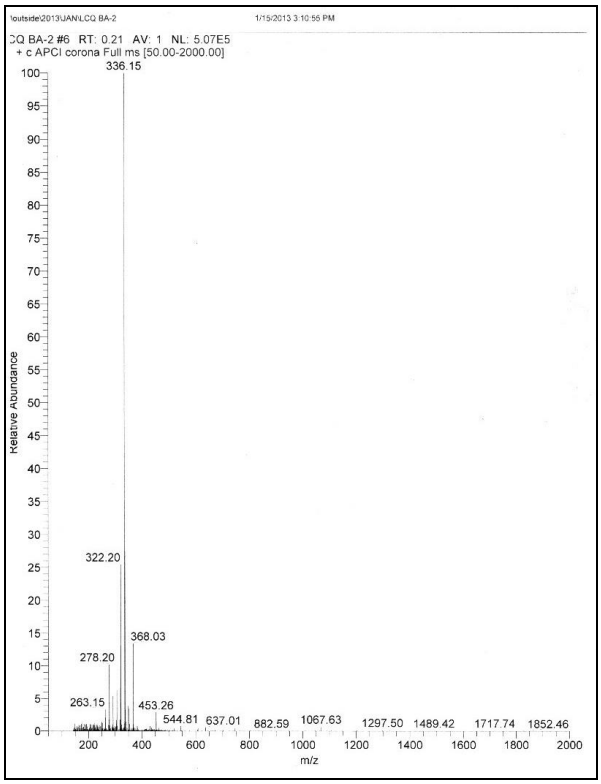


Fig. 3. Mass spectrum of berberine

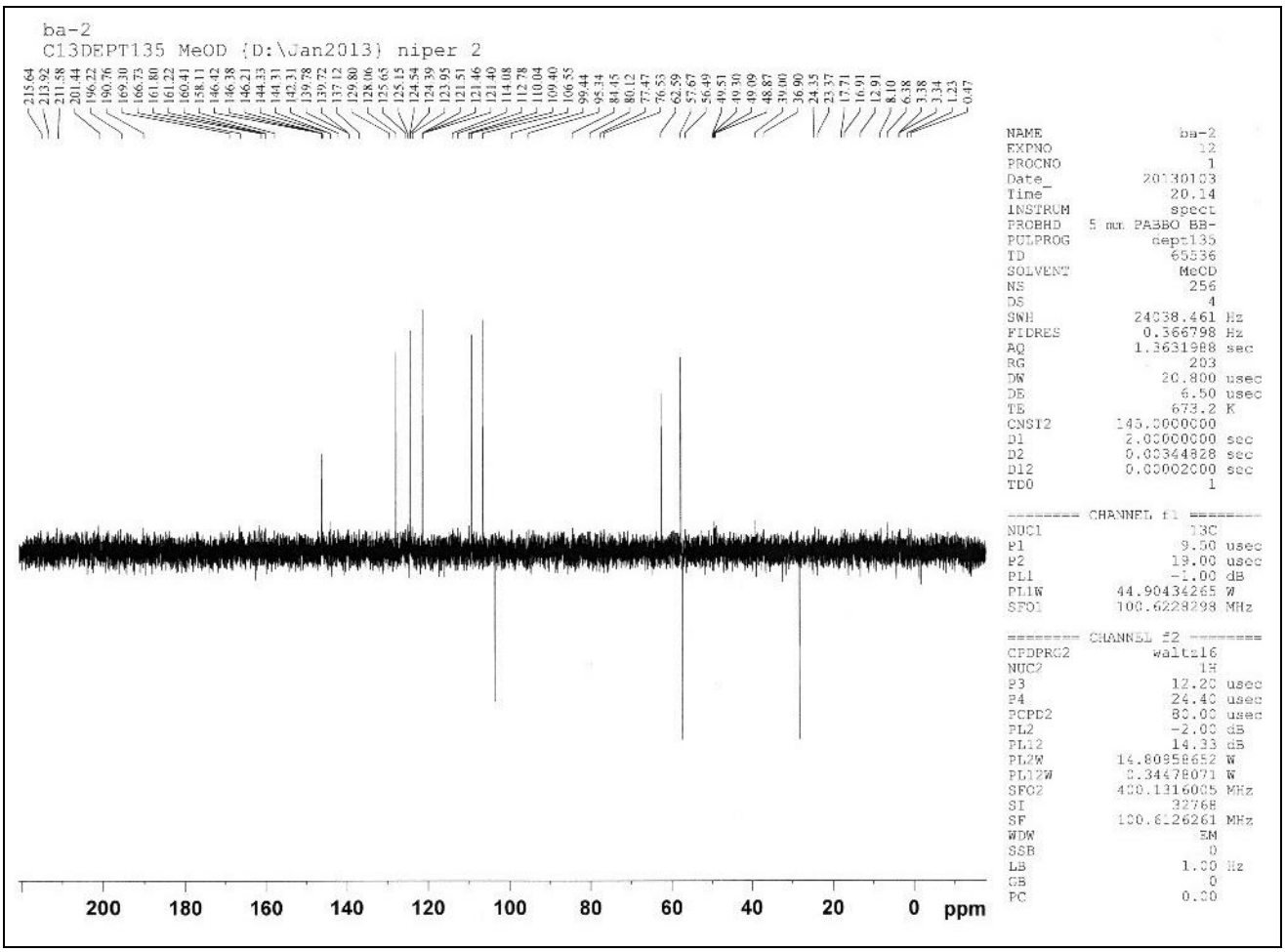


Fig. 4. DEPT (135) spectrum of berberine

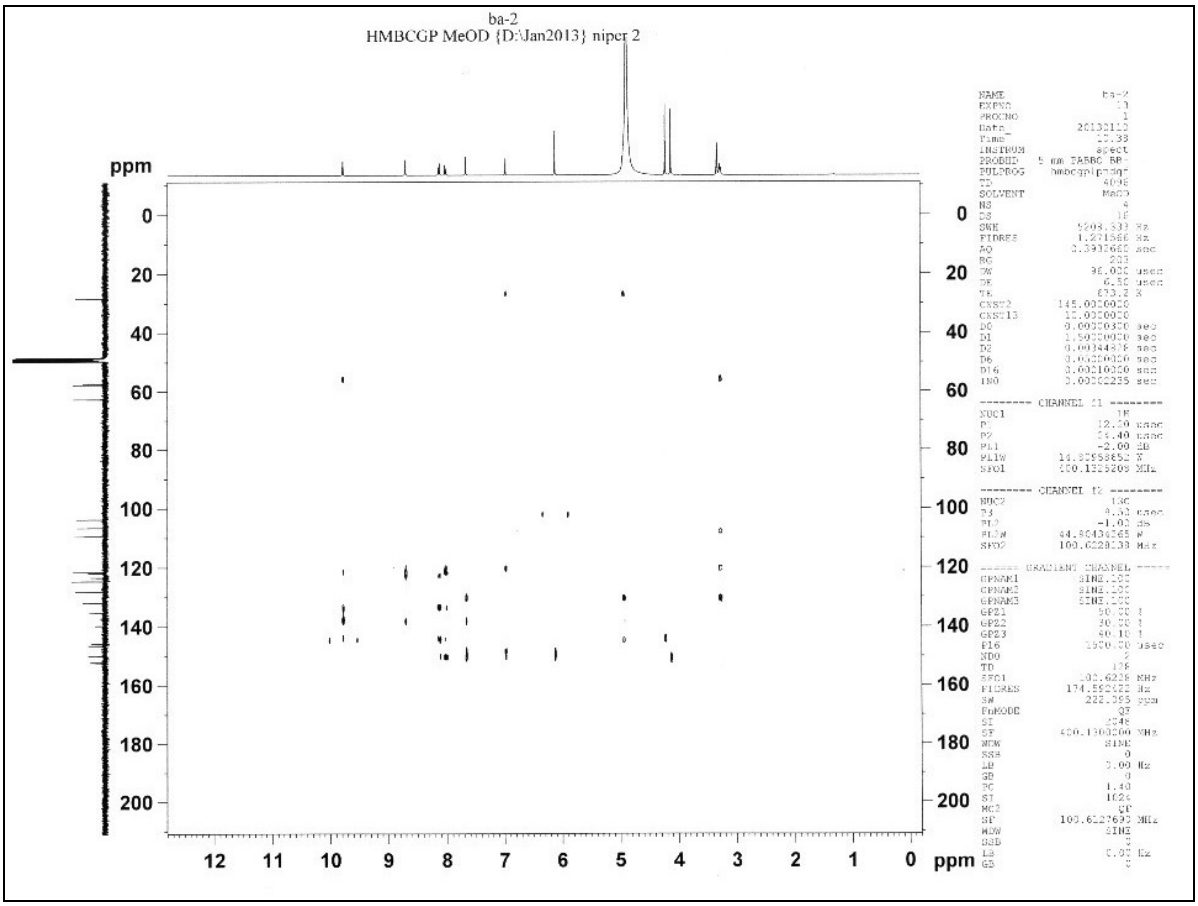


Fig. 5. HMBC spectrum of berberine

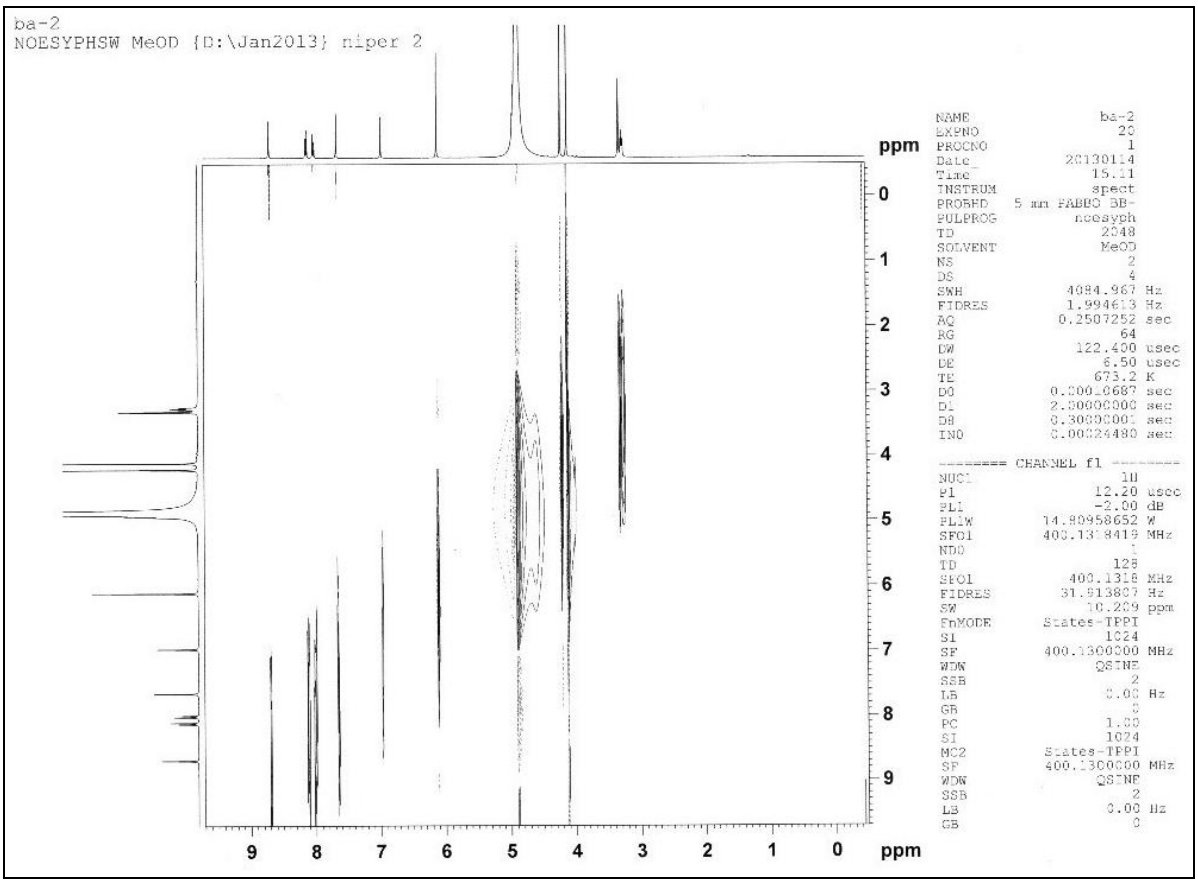


Fig. 6. NOESY spectrum of berberine

RESULTS AND DISCUSSION

Characterisation of berberine

The alkaloidal nature of berberine was determined with the help of Dragendorff and Wagner's reagents. Its melting point was measured to be 145 °C. Co-TLC of the compound with a market sample of berberine showed similar Rf value. The molar mass of the compound was found to 336 ($C_{20}H_{18}NO_4^+$) from a m/z value 336.15 (base peak) in its mass spectrum. Other intense peaks at 322 and 278 found in the MS were due to the loss of one CH_2 and two OCH_3 fragments respectively from m/z 336.

The ^1H NMR showed the signals at δ 7.6 (H-1), 7.0 (H-4), 3.2 (H-5), 4.9 (H-6), 9.8 (H-8), 8.0 (H-11), 8.1 (H-12), 6.1 (H-13), 8.7 (H-14), 4.2 (H-15) and 4.1 (H-16) ppm. The ^{13}C NMR exhibited signals at 121 (C-1), 132 (1a), 139 (C-2, -3), 122 (C-4), 128 (4a), 24 (C-5), 56 (C-6), 149 (C-8), 136 (C-8a), 146 (C-9), 147 (C-10), 109 (C-11), 123 (C-12), 124 (C-12a), 106 (C-13), 153 (C-13a), 103 (C-14), 162 (C-15) and 157 (C-16) ppm. The Distortionless Enhancement by Polarization Transfer (DEPT) spectra corroborated the presence of two primary, three secondary, six tertiary and nine quaternary carbons. Selected Correlation Spectroscopy (COSY), Heteronuclear Multiple Bond Correlation (HMBC) and Nuclear Overhauser Effect Spectroscopy (NOESY) correlations are shown in Fig. 7.

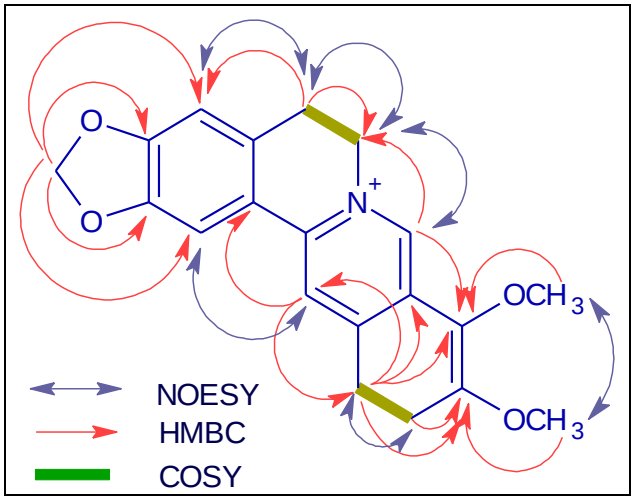


Fig. 7. Selected NOESY, HMBC and COSY correlations in berberine

Pharmacological relevance

Berberine has been found to exhibit activities against cancer, diabetes, cardiovascular disease, hyperlipidemia, inflammation, bacterial and viral infections, cerebral ischemia trauma, mental disease, Alzheimer disease and osteoporosis (Imenshahidi et al., 2016). Few selected pharmacological activities of berberine are shown below in following heads.

Anticancer activity

Berberine was found to serve as chemotherapy for the treatment of thyroid carcinoma and inhibit a wide range of proliferation of carcinoma cells (C643, OCUT1 and TPC1) along with the induction of mitochondrial apoptosis, G0/G1 cell cycle arrest and inhibitive migration whereas the normal human thyroid cells Htori3 were found less sensitivity to the cytotoxicity of berberine (Li et al., 2017). In colorectal carcinogenesis, berberine showed a reduction in the tumour of mice by 60%. The study revealed that it shows anti-proliferation activity by decreasing the azoxymethane initiated and dextran sulfate sodium-induced Ki-67 and COX-2 expression. It induces apoptosis in colorectal cancer cell lines and suppresses colon epithelial proliferation and tumorigenesis via AMPK dependent inhibition of mTOR activity. Berberine downregulated the downstream targets of mTOR 4E-binding protein-1 and p70 ribosomal S6 kinases and AMPK independent inhibition of NF-kB. It activated AMPK, inhibited mTOR and p65 phosphorylation and activated caspase-3 cleavage (Li et al., 2015).

Antidiabetic, antiobesity and antilipidemic activities

Therapeutically, berberine is recommended for the treatment of atherosclerosis and decreases metabolic endotoxemia in HFD- mice, tissue inflammation and restores gut barrier micthe robiota by increasing the intestinal expression of tight junction proteins and the thickness of the colonic mucus layer. Besides, it lowers arterial and intestinal expression of pro-inflammatory cytokines and chemokines (Zhu et al., 2018). It was found effective in metabolic syndrome associated with a high cardiovascular disease comprising dyslipidemia, obesity, high blood pressure and high blood glucose (Tabeshpour et al., 2017).

It lowers the cholesterol level, uric acid level, sanitising effects against insulin and hypoglycemic effect. In association with silymarin, it impran oves intestinal absorption and also found clinically effective for obese people with type 2 diabetes (Guarino et al., 2017). Via a post-transcriptional mechanism, it reduced the serum cholesterol, triglycerides and LDL-cholesterol of hypercholesterolemic patients and high-fat diet fed animals, and also increased hepatic LDLR mRNA and protein levels. The hypoglycemic action of insulin was found to enhance by berberine in diabetic animals. It works on multiple molecular targets as an inhibitor of α transcription activity and mRNA and protein levels of adipogenesis-related transcription factors PPARγ and C/EBPα and their upstream regulator, C/EBPβ. In addition, it inhibited the differentiation of 3T3-L1 diabetes-induced preadipocytes by suppressing the mitotic clonal expansion of 3T3-L1 preadipocytes (Huang et al., 2006; Choi et al., 2014).

Its anti-obesity effect has been attributed to the anti-adipogenic activity. It also suppresses the expressions of CCAAT/enhancer binding protein (C/EBP)α, peroxisome proliferators-activated receptor γ2 (PPARγ2) and other adipogenic genes. At the early stage of 3T3-L1 preadipocyte differentiation, it decreases the expression of cAMP response element-binding protein phosphorylation and C/EBPβ induced by 3-isobutyl-1-methylxanthine andthe forskolin (Zhang et al., 2015). Berberine increased the hepatic CD36 expression and triglyceride levels in mice (Choi et al., 2017). It promotes hepatic gene expression and circulating levels of FGF21 and ketone bodies in mice in a SIRT1-dependent manner to potentiate autophagy in the liver of high-fat, high-sucrose diet-fed obese mice. It acts in the liver to regulate lipid utilization and maintain whole-body energy metabolism. Hepatic lipid metabolism and energy expenditure in mice were found to be regulated by berberine inducing autophagy and FGF21 as there was a deficiencyan of the nutrient sensor SIRT1 in the liver of HFHS diet-fed obese mice and in mouse primary hepatocytes (Sun et al., 2018).

Berberine showed antidiabetic activity comparable to metformin. Its pharmacological mechanism revealed its effect as insulin mimetic and showed α-glucosidase reductase inhibition, the release of GLP 1, modification of gut microbiota and inhibition of enzyme dipeptidyl peptidase 4. It also has lipid-lowering action and is effective in polycystic ovarian disease (Patil et al., 2015). It serves as an activator of AMPK clinically and potentially used calorie restriction mimetics for extending healthspan; hence, it can be used as a potential candidate for the diabetes management (McCarty, 2014). It showed potential against metabolic syndrome by recovering the mitochondrial function associated with an increased activity of the mitochondrial sirtuin 3, normalizing mitochondrial function and preventing a state of the energetic deficit caused by impaired oxidative phosphorylation in the liver of high-fat fed rats (Teodoro et al., 2013). With its osteoclastogenesis decreasing property, berberine inhibits diabetic osteopath and reduces apoptotic pathways. In addition, it is helpful in lowering glucose level by stimulating glucagon-like peptide release and insulin sensitization thus exerting osteogenesis. Advanced glycation end-products (AGE) formation in diabetic condition is also decreased by berberine which ultimately helps to decrease the stiffness of collagen fibres. The molecule also has an inhibitory effect on parathyroid hormone and osteocalcin responsible for the osteoblastic activity (Rahigude et al., 2012).

The studies also found that berberine may ameliorate the development of insulin resistance by differentially preventing alterations in expression of IR, IRS-1, and glucagon in β-cells, α-cells, and hepatocytes (Gu et al., 2012). It prevents the development of obesity and insulin resistance, decreases food intake and increases the levels of serum lipopolysaccharide-binding protein, monocyte chemoattractant protein-1, and leptin. Besides, it decreases the serum level of adiponectin corrected for body fat in high-fat diet fed rats at 100 mg/kg body weight. Prevention of obesity and insulin resistance by berberine is at least partially mediated by structural modulation of the gut microbiota, which may help to alleviate inflammation by reducing the exogenous antigen load in the host and elevating SCFA levels in the intestine (Zhang et al., 2012).

A mechanism based study by Han et al. (2011) revealed that the antidiabetic effect of berberine is due to its efficacy in modulating the gut microbiota as it acts topically in the gastrointestinal tract and remains unabsorbed without systemic anti-infective activity. It upregulated peroxisome proliferator-activated receptor's α/δ/γ, cyclin-dependent kinase 9 and cyclin T1 mRNA and protein expression in adipose tissue, decreased tumour necrosis factor α and free fatty acid content and increased lipoprotein lipase activity in serum and adipose tissue (Zhou et al., 2010). It represses proinflammatory responses through AMPK activation in macrophages in adipose tissue of obese mice by downregulating the expression of proinflammatory genes such as TNF-α, IL-1β, IL-6, monocyte chemoattractant protein-1 (MCP-1), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). It suppresses the phosphorylation of MAPKs, such as p38, ERK, and JNK, and the level of ROS in macrophages (Jeong et al., 2009).

Berberine mimics insulin action and increases glucose uptake ability by 3T3-L1 adipocytes and L6 myocytes in an insulin-independent manner, inhibiting phosphatase activity of protein tyrosine phosphatase 1B (PTP1B), and increasing phosphorylation of IR, IRS1 and Akt in 3T3-L1 adipocytes. In diabetic mice, it lowers glucose level and improves impaired glucose tolerance, but does not increase insulin release and synthesis (Chen et al., 2010). It protects against hyper-glycemia-induced endothelial injury and enhances the endothelium-dependent vasodilatation, which is mediated in part through activation of the AMPK signalling cascade. Berberine enhances the phosphorylation of endothelial nitric oxide synthase (eNOS) at Ser1177. High glucose-induced generation of ROS, cellular apoptosis, nuclear factor-κB activation, and expression of adhesion molecules were found to attenuate by this molecule. Moreover, it elicits endothelium-dependent vasodilatations and alleviates high glucose-mediated endothelial dysfunction in mouse aortic rings (Wang et al., 2009). Berberine improves lipid dysregulation and fatty liver in obese mice through central and peripheral actions. It reduced liver weight, hepatic and plasma triglyceride, and cholesterol contents in the mice, and promoted the AMPK activity and fatty acid

oxidation which contributed to its change of gene expression involved in lipid metabolism (Kim et al., 2009). It reduces body weight, plasma triglycerides and improves insulin action, glucose tolerance without altering food intake in mice. It down-regulates the expression of genes involved in lipogenesis and upregulates those involved in energy expenditure in adipose tissue and muscle. An increase of AMP-activated protein kinase activity in 3T3-L1 adipocytes and L6 myotubes, increased GLUT4 translocation in L6 cells in a phosphatidylinositol 3′ kinase-independent manner and reduction of lipid accumulation in 3T3-L1 adipocytes was also recorded after treatment with berberine (Lee et al., 2006).

Anti-inflammatory activity

Berberine inhibits TNF-α, IL-1β, and IL-6 expression through AMP-activated protein kinase activation in BV-2 microglia and downregulates LPS- or interferon-γ-induced nitric oxide synthase (iNOS) and cyclo-oxygenase-2 (COX-2) expression in BV-2 microglia cells. It was found to suppress the phosphorylated of ERK but not p38 and JNK in BV-2 microglia. It also induces AMPK signalling pathways activation involved in anti-neuroinflammation (Lu et al., 2010).

CONCLUSION

Berberine, a natural quaternary alkaloid was found to decrease blood sugar and manage the type 2 diabetes via various pathways including the suppression of phosphorylation of MAPKs and level of reactive oxygen species. Its role against the tumours and inflammation was also proved by the research. However, its bioavailability is low, it can be developed as an antidiabetic drug by improving its bioavailability.

ACKNOWLEDGMENT

This work was financially supported by University Grants Commission, New Delhi (India) under Dr DS Kothari Postdoctoral Scheme [Grant No. F.4-2/2006(BSR)/13-460/2011(BSR)].

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

Chandel S, Bagai U, Semwal RB, Semwal DK (2015). Antiplasmodial activity of aqueous extract of Berberis aristata roots against Plasmodium berghei-infected BALB/c mice. Pharmaceutical Biology, 53, 1735-1740.

Chen C, Zhang Y, Huang C (2010). Berberine inhibits PTP1B activity and mimics insulin action. Biochemical and Biophysical Research Communications, 397, 543-547.

Choi JS, Kim JH, Ali MY, Min BS, Kim GD, Jung HA (2016). Coptis chinensis alkaloids exert anti-adipogenic activity on 3T3-L1 adipocytes by downregulating C/EBP-α and PPAR-γ. Fitoterapia, 98, 199-208.

Choi YJ, Lee KY, Jung SH, Kim HS, Shim G, Kim MG, Oh YK, Oh SH, Jun DW, Lee BH (2017). Activation of AMPK by berberine induces hepatic lipid accumulation by upregulation of fatty acid translocase CD36 in mice. Toxicology and Applied Pharmacology, 316, 74-82.

Cicero AFG, Derosa G, Maffioli P, Reggi A, Parini A, Rosticci M, Grandi E, Borghi C (2013). Berberine induced improvement in Hepatic Steatosis Index in overweight dyslipidaemic patients treated with lipid-lowering nutraceuticals. Current Topics in Nutraceuticals Research, 11, 41-45.

Dewick P (2009). Medicinal Natural Products: A Biosynthetic Approach (3rd ed.). West Sussex, England: Wiley, pp. 357-358.

Gu JJ, Gao FY, Zhao TY (2012). A preliminary investigation of the mechanisms underlying the effect of berberine in preventing high-fat diet-induced insulin resistance in rats. Journal of Physiology and Pharmacology, 63, 505-513.

Guarino G, Strollo F, Carbone L, Della TC, Letizia M, Marino G, Gentile S (2017). Bioimpedance analysis, metabolic effects and safety of the association Berberis aristata/Bilybum marianum: a 52-week double-blind, placebo-controlled study in obese patients with type 2 diabetes. Journal of Biological Regulators and Homeostatic Agents, 31, 495-502.

Han J, Lin H, Huang W (2011). Modulating gut microbiota as an anti-diabetic mechanism of berberine. Medical science monitor: International Medical Journal of Experimental and Clinical Research, 17, RA164.

Huang C, Zhang Y, Gong Z, Sheng X, Li Z, Zhang W, Qin Y (2006). Berberine inhibits 3T3-L1 adipocyte differentiation through the PPARγ pathway. Biochemical and Biophysical Research Communications, 348, 571-578.

Imenshahidi M, Hosseinzadeh H (2016). *Berberis vulgaris* and berberine: an update review. Phytotherapy Research, 30, 1745-1764.

Jeong HW, Hsu KC, Lee JW, Ham M, Huh JY, Shin HJ, Kim WS, Kim JB (2009). Berberine suppresses proinflammatory responses through AMPK activation in macrophages. American Journal of Physiology-Endocrinology and Metabolism, 296, E955-E964.

Kim WS, Lee YS, Cha SH, Jeong HW, Choe SS, Lee MR, Oh GT, Park HS, Lee KU, Lane MD, Kim JB (2009). Berberine improves lipid dysregulation in obesity by controlling central and peripheral AMPK activity. American Journal of Physiology-Endocrinology and Metabolism, 296, E812-E819.

Komal S, Ranjan B, Neelam C, Birendra S, Kumar SN (2011). *Berberis aristata*: A review. International Journal of Research in Ayurveda and Pharmacy, 2, 383-388.

Lee YS, Kim WS, Kim KH, Yoon MJ, Cho HJ, Shen Y, Ye JM, Lee CH, Oh WK, Kim CT, Hohnen-Behrens C, Gosby A, Kraegen EW, James DE, Kim JB (2006). Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. Diabetes, 55, 2256-2264.

Li L, Wang X, Sharvan R, Gao J, Qu S (2017). Berberine could inhibit thyroid carcinoma cells by inducing mitochondrial apoptosis, G0/G1 cell cycle arrest and suppressing migration via PI3K-AKT and MAPK

signaling pathways. Biomedicine & Pharmacotherapy, 95, 1225-1231.

Li W, Hua B, Saud SM, Lin H, Hou W, Matter MS, Jia L, Colburn NH, Young MR (2015). Berberine regulates AMP-activated protein kinase signaling pathways and inhibits colon tumorigenesis in mice. Molecular Carcinogenesis, 54, 1096-1109.

Liu F, Gan PP, Wu H, Woo WS, Ong ES, Li SFY (2012). A combination of metabolomics and metallomics studies of urine and serum from hypercholesterolaemic rats after berberine injection. Analytical and Bioanalytical Chemistry, 403, 847-856.

Lu DY, Tang CH, Chen YH, Wei IH (2010). Berberine suppresses neuroinflammatory responses through AMP-activated protein kinase activation in BV-2 microglia. Journal of Cellular Biochemistry, 110, 697-705.

McCarty MF (2014). AMPK activation—protean potential for boosting healthspan. Age, 36, 641-663.

Mokhber-Dezfuli N, Saeidnia S, Gohari AR, Kurepaz-Mahmoodabadi M (2014). Phytochemistry and Pharmacology of Berberis Species. Pharmacognosy Reviews, 8, 8–15.

Parmar C, Kaushal MK (1982). *Berberis aristata*. Wild Fruits. New Delhi, India: Kalyani Publishers. pp. 10–14.

Patil T, Patil S, Patil A, Patil S (2015). Is berberine superior to metformin in management of diabetes mellitus and its complications? International Journal of Pharmacognosy and Phytochemical Research, 7, 543-553.

Rahigude AB, Kaulaskar SV, Bhutada PS (2012). Possible therapeutic potential of berberine in diabetic osteopathy. Medical Hypotheses, 79, 440-444.

Semwal RB, Semwal DK, Kapoor P (2012). Dyeing properties of Berberis aristata DC with natural and synthetic mordants. Trends in Applied Sciences Research, 7, 392–399.

Singh J, Kakkar P (2009). Antihyperglycemic and anti-oxidant effect of *Berberis aristata* root extract and its role in regulating carbohydrate metabolism in diabetic rats. Journal of Ethnopharmacology, 123, 22-26.

Srivastava S, Rawat AKS (2013). Quality evaluation of ayurvedic crude drug daruharidra, its allied species, and commercial samples from herbal drug markets of India. Evidence-Based Complementary and Alternative Medicine, 2013, 472973.

Sun Y, Xia M, Yan H, Han Y, Zhang F, Hu Z, Cui A, Ma F, Liu Z, Gong Q, Chen X, Gao J, Bian H, Tan Y, Li Y, Gao X (2018). Berberine attenuates hepatic steatosis and enhances energy expenditure in mice by inducing autophagy and fibroblast growth factor 21. British Journal of Pharmacology, 175, 374-387.

Tabeshpour J, Imenshahidi M, Hosseinzadeh H (2017). A review of the effects of Berberis vulgaris and its major component, berberine, in metabolic syndrome. Iranian Journal of Basic Medical Sciences, 20, 557-568.

Teodoro JS, Duarte FV, Gomes AP, Varela AT, Peixoto FM, Rolo AP, Palmeira CM (2013). Berberine reverts hepatic mitochondrial dysfunction in high-fat fed rats: a possible role for SirT3 activation. Mitochondrion, 13, 637-646.

Wang Y, Huang Y, Lam KS, Li Y, Wong WT, Ye H, Lau CW, Vanhoutte PM, Xu A (2009). Berberine prevents hyperglycemia-induced endothelial injury and enhances vasodilatation via adenosine monophosphate-activated protein kinase and endothelial nitric oxide synthase. Cardiovascular Research, 82, 484-492.

Zhang J, Tang H, Deng R, Wang N, Zhang Y, Wang Y, Liu Y, Li F, Wang X, Zhou L (2015). Berberine suppresses adipocyte differentiation via decreasing CREB transcriptional activity. PLoS One, 10, e0125667.

Zhang X, Zhao Y, Zhang M, Pang X, Xu J, Kang C, Li M, Zhang C, Zhang Z, Zhang Y, Li X, Ning G, Zhao L (2012). Structural changes of gut microbiota during berberine-mediated prevention of obesity and insulin resistance in high-fat diet-fed rats. PloS one, 7, e42529.

Zhou J, Zhou S (2010). Berberine regulates peroxisome proliferator-activated receptors and positive transcription elongation factor b expression in diabetic adipocytes. European Journal of Pharmacology, 649, 390-397.

Zhu L, Zhang D, Zhu H, Zhu J, Weng S, Dong L, Liu T, Hu Y, Shen X (2018). Berberine treatment increases Akkermansia in the gut and improves high-fat diet-induced atherosclerosis in Apoe−/− mice. Atherosclerosis, 268, 117-126.

How to cite this article?

Semwal RB, Semwal DK, Aswal S, Kumar A (2018). Spectral studies and pharmacological relevance of berberine isolated from *Berberis aristata* roots. Current Medical and Drug Research, 2 (1), Article ID 181.

*****