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A Laconic Review on Extraction, Biological Activities of Herbal Formulations of Berberine: A Traditional Drug

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ABSTRACT

Herbal formulation dosage form consists of one or more herbs processed in specified quantities to provide specific nutritional, cosmetic benefits use to diagnose the disease. Herbal formulations contain an active substance and preparation in combination of one or more herbal compounds. *Berberis aristata* is one of herbs of an ancient Ayurveda medicine and different properties along with various treatment of illness. Berberine, is a type of alkaloid which is quarternary protoberberine, is one of the known bioactive compounds scattered extensively in a number of clinically significant medicinal plants such as *Hydrastis canadensis* L., *Phellodendron amurense* R. ,*Coptis japonica* M., and Berberine containing plants have been used in traditional and folk medicine around the globe for centuries. It has been used for a, anti-pyretic diarrhea, bitter tonic, and eye infections. In the past three eras, Berberine has been studied intensively in over thousands cases because of its therapeutics, physicochemical effects, pharmacological, and physiological effects such as cardiovascular, anti-inflammatory, anti leshmanial, and anti- secretory, effects. Berberine act as a phytoconstituents in formulations and available in ayurveda, allopathy, and homeopathy medicines. With this review, we will evaluate the various traditional and medicinal use of Berberine and their isolation and extraction procedure. We will also review the potential of this plant as various dosage forms for the treatment of various diseases.

Keywords: Berberine; Extraction Method; Isolation method; Skin problems

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INTRODUCTION

Now-a-days herbal medicines are widely used and recommend for the treatment of patients health care. Herbal formulation dosage form consists of one or more herbs processed in specified quantities to provide specific nutritional, cosmetic benefits use to diagnose the disease.[1] Herbal formulations contain an active substance and preparation in combination of one or more herbal compounds. Herbal formulations are obtained by extraction, distillation, expression, purification, fractionation include powdered of various crude plants.[2]

Herbal formulations are inexpensive, and possess good therapeutic action, better for patients' health care. Herbal formulations have no or less side effects as compared to allopathic or other systems. Herbal formulation is used in the treatment of medical conditions, enhancement of bioavailability, pharmacological activity and solubility.[3]

Ayurveda is a traditional system and improve physical, mental and emotional support for patients. Ayurveda is an ancient medicine healing system. It was developed more than 3000 years ago in India. Ayurveda helps to improve good health, cure disease, preventing and treating disease illness. Ayurveda believe in five basic elements found in universes such as space, air, fire, water and earth and human body systems supports three life energies or forces are known as doshas. Doshas are known as Vata dosha, Pitta dosha and Kapha dosha each controls in different body systems.[3]

Berberis aristata is one of herbs of an ancient Ayurveda medicine and different properties along with various treatment of illness. Berberine is an active phytoconstituents which is available in ayurveda, allopathy, and homeopathy medicines. The whole part of plant is also good source of dye and tannins. Berberine is main chemical constituents having various pharmacological actions. It is an active constituent

benzylisoquinoline alkaloid and used in Ayurvedic and Chinese systems.[4-5]

This review evaluates various pharmacological traditional properties of Berberine along with their extractions method and potential use in the treatment of psoriasis and other disease.

BASIC PROPERTIES AND USE OF BERBERINE

The basic properties of Berberine were shown in Table 1. The chemical structure of Berberine is represented in Figure 1. Berberine has various biological and traditional uses which are listed in the Table 2. Berberine was intensively used in the skin disorders and the whole information regarding their uses in skin disorders are listed in the Table 3.

Table 1: Basic properties of Berberine

Sr. no.	Basic properties	
1	Chemical formula	$C_{20}H_{18}NO_4^+$
2	Molecular mass	336.366gmol^{-1}
3	Structure name	5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium (quaternary amine)
4	Basic nucleus	Quaternary benzylisoquinoline alkaloid molecule
5	Nature	Non basic
6	Appearance	Yellow solid
7	Melting point	145°C
8	Solubility	Poor water soluble
9	Salt	Water, acidic, neutral media
10	Base	Soluble in organic solvents

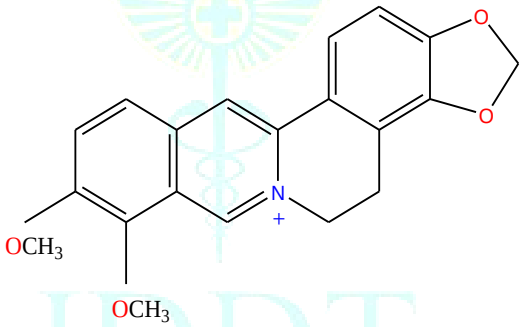

Figure 1: Berberine

Table 2: Biological and traditional uses of plants

Sr. no.	Biological name	Plant name	Traditional uses
1	*Berberis vulgaris*	Barberry	Acne, inflamed bumps, pimples, cardiovascular and hypertension
2	*Argemone mexicana*	Prickly poppy	Malaria, jaundice, snake bites
3	*Berberis aristata*	Turmeric	Antibacterial, anti-diarrheal and anticancer
4	*Mahonia aquifolium*	Oregon grape	Eczema, tuberculosis, periodontitis, dysentery, wounds.
5	*Hydrastis canadensis*	Goldenseal	As astringent, bitter tonic, laxative, antidiabetic and muscular stimulant
6	*Eschscholzia californica*	Californian poppy	Depression, nerve pain, psychiatric conditions, blood vessel problems and sedation
7	*Xanthorhiza simplicissima*	Yellow root	Anti-inflammatory, astringent, antimicrobial, anticonvulsant and immunostimulant
8	*Phellodendron amurense*	Amur cork tree	Osteoarthritis, weight loss and obesity, diarrhea, ulcers in stomach, diabetes, pneumonia, anti-inflammatory activity
9	*Coptis chinensis*	Chinese goldthread	Dye, wool and fibers
10	*Tinospora cordifolia*	Heart-leaved moonseed	Gout, lymphoma, rheumatoid arthritis, peptic ulcer, cancers and immune system

Table 3: Berberine species uses in intestinal and skin disorder

Berberine species	References (work done)	Berberine used in intestinal disorders	Berberine used in skin disorders
In the Berberidaceae family, they used as raw material and an important ingredient used in Ayurvedic traditional medicine and Chinese medicine. Berberis genus includes 450–500 species which represent the most natural supply of Berberine. The plants which are related genus are commonly used as various activities. The Berberine fruit (*Berberine vulgaris*) is used as blood purifying agent from the past years. Use of stem, root, bark of plant rich in Berberine. Berberis species history has quite 3000 years.	(Karimov, A. et al., 1993, ; Birdsall, T.C. et al., 1997; Gupta, A. et al., 2014; Tandon, R. et al., 2004 Singh, A. et al., 2010; Amritpal, S. et al., 2010; Kulkarni, S.K. et al., 2009)[6-12]	Treat hepatitis A, hepatitis B, hepatitis C and hepatitis D, prostate cancer, syphilis, poliomyelitis, conjunctivitis, leishmaniasis, blood vomiting, jaundice, rheumatism, body pains, sleeping sickness, treated infectious disease such as urinary tract infection, HIV sexual asthenia, diabetes, hypertension, hemostatic, intestinal spams, intestinal worms, fatigue, constipation, dysentery, ulcer, intercostals pain, spleen in children, sore, Treat various fevers: yellow fever, rickettsia fever, typhoid fever, chills, antipyretic, malaria, Tuberculosis, coughs.	In inflammation condition, infectious disorder on skin, anti-diabetes, aches, wounds, skin ailments.

EXTRACTION METHOD

(Marek, R. et al., 2003; Grycova, L. et al., 2007) they reported that the Berberine are protoberberine alkaloid salts and they are changed in specific types of bases and extract further extracted in organic solvents. Berberine using classical extraction used different solvents e.g. acidified, aqueous mixtures, chloroform, ethanol and methanol. Sensitivity was major challenged for Berberine extraction and degrade Berberine light and also in case high temperature.[13-14]

(Babu, N.H.R. *et al.*, 2012) they reported that they represent extraction process and drying temperature sample serious factor. Berberine found plant part of stem from *Cosinium fenestratum* and collect sample for the Berberine and extract yield from tissue sample was dried different types:

(i) Cold extraction method: in this method sample dried under refrigerator conditions (-20°C) with methanol and ethanol. [15]

(ii) Hot extraction method: in this method sample dried in water bath (50°C) with ethanol and methanol.

Extract centrifuged and dried at constantly room temperature and filtered berberine sample analyzed.[15]

(Teng, H. *et al.*2013; Choi, Y. *et al.,* 2013) they reported that the serious stage choice of solvents considered in Berberine. The solvents used mostly for the extraction process aqueous, acidified, methanol, ethanol and alkaloid rhizomes of coptis chinensis content Berberine extract. The acidified solvents (hydrochloride acid, phosphoric acid, nitric acid, sulfuric acid and acetic acid) used with combination higher solubility with free alkaloid base salts and concentration 0.34% phosphoric acid compared with classical extraction techniques. The extraction by the reflux and soxhlet method of Berberine at higher amount of yield contain by cold acid extraction.[16]

(Mokgadi, J.*et al.*, 2013; Rojsanga, P.*et al.,* 2005; Gritsanapan, W.*et al.*, 2005) they reported that drawbacks of conventional methods and longtime extraction with large amount of solvents. They used maceration process procedure for the part of plant *Coscinium fenestratum*with total 3200ml ethanol solvent (80%) long time period.[17-18]

(Rojsanga, P.*et al.,* 2006; Gritsanapan, W.*et al.,* 2006) they reported that the used different extraction classical extraction as soxhlet, percolation and maceration techniques. The Berberine contain from stem part of plant *Coscinium fenestratum* lower amount as compared to previous study. The extract material used 30g and solvents used 2000ml amount for maceration process, 600ml amount used for soxhlet extraction and 5000ml amount used for percolation extraction process. The extraction continued 7 days long time periods for the process maceration and soxhlet extraction process working 3 days.[19]

(Shigwan, H.*et al.*, 2013) they reported that a large amount solvent was used in conventional hot extraction methods. The Berberine obtained stem bark from *Berberis aristata* and *Berberis tinctoria* was used 800g with 2500ml methanol in temperature 50°C for 3 hr. The extraction method widely used traditional method to extract out of Berberine and variety method used for development. To improvement efficiency of extraction, decreased time consumed for extraction and amount of solvents used within extraction. Better results by used different extraction techniques found successfully. These methods are alternative techniques (MAE, PLE, SFE, UPE and USE) with compared with method of classical extraction.[20]

(Alupului, A.*et al.,* 2009) they reported that ultrasonically extraction and microwave-assisted extraction was considered in efficient, simple method, and cheap cost techniques.[21]

(Chang, Y.*et al.,* 2013) that was performed in lesser extraction time. In his procedure were used to selected combination ionic liquid, green solvents solutions and the extract *Coptis chinesis* contain Berberine by using USE method technique.[22]

(Xu, K.*et al.,* 2018) they reported that the compared many extraction methods such as soxhlet extraction and distillation extraction collect phellodendrine to establish in proper manner high efficient method. The extraction of phellodendron fresh bark from Cortex phellodendri contains

Berberine extract. In his case, Berberinein combination of solvents used methanol, ethanol, acidified solvents and water with the extraction contain higher amount of extraction yield. They was determined that Berberine extract use of hydrochloride acidified acid, methanol and USE technique much more efficient. They concluded that the higher yield extraction compared with soxhlet method and distillation method of Berberine.[23]

(Xi, J.*et al.,* 2017) they reported that the classical extracted method technique was considered. This technique present many advantages increased the yield, extraction time reduce, quality enhanced and reduced solvent consumption.[24]

(Guoping, L. *et al.,* 2012) they reported that the *Cortex phellodendri* made comparison with different extraction techniques; heat reflux, MAE, UPE and USE techniques. The yield was obtained by extraction method in case UPE with lower extraction time and higher extraction time. Reflux, MAE and USE with 5.35mg/g for 2 hrs, 5.61mg/g for 1 hrs and 6mg/g for 15min.[25]

(Mustafa, A.*et al.,* 2011 ;Turner, C.*et al.,* 2011) they reported that the considered both extraction method pressurized method and other method used accelerated solvent extraction. The plant extraction used as a technology for compound to pressurized liquid extraction and pressurized fluid extraction.[26] The various methods of extraction of Berberine are listed in the Table 4.

Table 4: Various methods of extraction of Berberine from various crude drugs

Sr. no.	Crude drug	References	Method extraction and Isolation	Method of analysis various analytical techniques
1	*Argemone mexicana*	(Samal, P.K. *et al.,*2013)[27]	Method- Soxhlet extraction Solvents: methanol Dry the compound by evaporation and Re-solubilized the dried compound in methanol with required concentration.	Method- HPTLC Stationary Phase: silica gel (60F254) Mobile phase: Toluene: Ethyl acetate (9:3, v/v). Detection of compound at : 266 nm
2	*Berberis aristata* DC 1.5g and herb extract 0.1 g	(Singh, R. *et al.,*2010)[28]	Method- Reflux isolation Solvents for extraction: Take 100 mL methanol on a water bath for 1 hr. Filter process- Re-isolate the crude by use of ES in 50 ml volume and repeat the procedure2 times for 30 min. Filtrates combination and concentration to 50ml Herb extracts Method- ultrasonic extraction Solvents: Methanol Volume: 10 mL approx. Sonication process and Filtration process is done.	Method- HPLC Column: Zorbax ODS II, 250 x 4.6mm (5µm) Mobile phase: potassium hydrogen phosphate buffer (pH 2.5). Detection at: 346 nm Temperature: 40°C Flow Rate: 1 ml/min Method- Herbal ultrasonic extraction process Solvents used: methanol (Volume 25ml minimum) Sonication process.
3	*Berberis aristata,* *Berberis tinctoria*	(Shigwan, H.*et al.,* 2013)[20]	Method: Hot extraction process Solvents Used: methanol (2.5 Litre) Time: Min. 3 hr Temperature: 50°C	Method- HPLC Column: Unisphere is used (C18, 150 x 4.6mm or 5µm) Mobile Phase: 0.1% (trifluoroacetic acid) Acetonitrile in the ratio of (60:40v/v) Detection at: 350 nm Temperature: 30°C Flow Rate: 1 ml/min
4	*Coptis chinensis*	(Teng, H, Choi, Y.*et al.,* 2013)[16]	Method- Acid assisted extraction process.	Method- HPLC Column used: XTerra (C18, 250 x 4.6mm)

			Solvents used: Inorganic acids eg: HCL Phosphoric acid, nitric acid, and sulfuric acid) and one Organic acid eg: Acetic acid Time:1 to 8 hr, Concentrations Range of acid: 0 to1% Ratios: 20 to 60 mL/g Maceration temp.: 25°C Filtration: Final volume is diluted with 100 mL Method- Soxhlet extraction process Solvents used: ethanol Time: 4 hr Temperature: 70°C Dry the extract by evaporation and Re-solubilized in100ml Method- Heating reflux extraction process Solvents used: ethanol Soaking time: 1 hr Extraction time: 4 hr Temperature: 70°C on water bath Filtration: Dilute with 100 mL.	Mobile phase used: Acetonitrile Potassium dihydrogen phosphate Ratio: (27:75 v/v) Detection at: 345 nm Temperature: 30°C
5	*Cortex phellodendri*	(Guoping, L.*et al.,* 2012)[25]	Method- Ultrahigh pressure extraction (UPE) Parameters used: Solvents used: ethanol Ratio of liquid-solid: 31.3 Pressure of extraction: 243.30 Time: 2 min	Method- HPLC Column Used: Hypersil Oxidative Desulfurization (C18, 250 × 4.6mm and 5µm) Mobile Phases used: triethanolamine Solution pH: 3.5 Detection at: 265 nm Temperature: 30°C Flow Rate: 1 ml/min
6	*Coptis rhizome*	(Liu, B.*et al.,*2006)[29]	Method: Supercritical fluid extraction process Time: More than 3 hr Temperature: 60°C Pressure range: 200- 500 bar Flow-rate of CO: 1 Litre/min Flow-rate of modifier system: 0.4 mL/min. Organic solvent: ethanol carbon dioxide, methanol	Methods: HPLC Column Used: Diamonsil (C18, 250 × 4.6mm and5µm) Mobile Phases used: Potassium di-hydrogen phosphate : Acetonitrile Detection at: 345 nm Flow rate: 1 ml/min

			Tween Soxhlet extraction: Extraction Solvents: hydrochloric acid: methanol (1: 100, v/v) Time: 8 h	
7	*Cortex pellodendri* *Amurensis*	(Liu, S.*et al.,* 2013)[30]	Method: Ultrahigh pressure extraction Solvents used: ethanol Ratio of liquid-solid : 30: 1 Extracting pressure : 400 MPa Time:4min Temperature : 40°C Method: Ultrasonic extraction process Solvents used: ethanol Soaking time for sample: 24 hr Sonication time: 60 min Temperature: 30°C Method- Heat reflux extraction process Solvent used: ethanol Soaking time for sample: 24 hr Extraction time: 4 hr Method- Soxhlet extraction process Solvent used: ethanol Soaking time: 4 hr Time of sample isolation: 4 hr	Method: HPLC Column used: Daisopak (SP-120-5-ODS_BP, 250 × 4.6mm and5µm) Mobile Phases used: Acetonitrile phosphoric acid water ratio: [0.7:100 v/v] Detection at: 345 nm Temperature: 25°C Flow Rate: 1 mL/min
8	*Coscinium fenestratum*	(Rojsanga, P.*et al.,*2005; Gritsanapan, W.*et al.,* 2005)[18]	Method: Maceration Extraction process Solvents used: ethanol Shaking time: 80 hr rpm-200 Re-extraction time: 48 hr Shaking time: 24 hr Combination of extracts concentration Dryness: By evaporation) Re-solubilized: 10 mg dried extract in ethanol	Method: TLC Stationary phase used: Silica gel (GF254) Mobile phase used: ethyl acetate: butanol: formic acid :water (50:30:12:10) Detection at: 366 nm
9	*Coscinium fenestratum*	(Arawwawala, L.D.*et al.,*2012; Wickramaar , W.A.*et al.,*2012)[31]	Solvent used: methanol Extraction (Hot): sample refluxed with solvent upto3 hr Filtration: Methanol Evaporation: Methanol. Extracts Re-solubilized in: Methanol Method: Cold extraction process Solvent used: ES Time: 24 hr Filtration/evaporation	Method: TLC Adsorbent used: Silica Gel (GF-254) Solvent used: n-Butanol: Ethyl acetate: Acetic acid Ratio: (2.5:1.5:1, v/v/v) Detection at: 254 and 366 nm

			/Resolubilization: Methanol	
10	Dried powder stem *Coscinium fenestratum*	(Akowuah, G.A.*et al.,*2014; Rojsanga, P. et al., 2010)[32-33]	Solvents used: water/ methanol/water (1:1:1 v/v) Methanol Sonication time: 15 minTemperature: room temp. Centrifugation process: 2800 rpm for 15min. Filtration/evaporation/ Resolubilization: Methanol:water Ratio: 9:1 v/v	Method- HPLC Column used: (Oxidative Desulfurization, Chromolith, RP-18e,100 × 4.6mm) Mobile Phases used: Methanol Deionized Ratio: Water (90:10 v/v) Flow rate: 0.5 mL/min Temperature: 25°C Detection: UV
11	Dried form *Coscinium fenestratum*	(Babu, N.H.R.*et al.,*2012)[15]	Method- Cold extraction process Temperature: 20°C Hot extraction temperature: 50°C on water bath Solvent used: ethanol Centrifugation time: 10 min Temperature: 10°C Samples	Method: HPLC Column used: (C18, 250 × 4.6mm and 5µm) Mobile Phases used: Acetonitrile Trifluro-acetic acid Ratio (50:50, v/v) Detection at: 344 nm Flow rate: 0.8 ml/min
12	Goldenseal, *Hydrastis canadensis*	(Mokgadi, J.*et al.,* 2013)[17]	Method: Pressurized hot water extraction process Solvent used: water Temperature:140°C **Parameters used:** Pressure: 50 bars Flow rate: 1mL/min Time: 15min Method: Reflux extraction process Solvent used: methanol Sonication time: 4 hr Sonication temperature: 80°C Method: Ultrasonic extraction process Solvent used: Methanol Reflux time: 6 hr by continuously stirring process.	Method: HPLC (Diode Array Diode) Column used: Zorbax eclipse Plus (C 18, 75 x 4.6mm and 3.5µm) Mobile phase used: Formic Acid- pH 2.7 Methanol Detection at: 242 nm Temperature: 35°C Flow rate: 1 ml/min MS Detection by: Elect spray ionization (+) Temperature of capillary: 200°C Current: 20 V Voltage of tube lens: 5V
13	Root *Berberis aristata* DC	(Patel, M.C.*et al.,*2013)[34]	Method: Soxhlet extraction process Solvent used: Ethanol is used to form an extract. Desolvation: hot water filtration: hot water Acidification: HCL Cool at: ice bath Cooling time: 30min Eg: overnight in a refrigerator	Method: HPTLC Stationary phase used: Pre-coated silica gel Grade: 60GF-254 Mobile phases used: n-butanol and glacial acetic acid or water Ratio: (12:3:4 v/v/v) Temperature: 33 ± 5°C Detection at: 350 nm
14	Rabbit plasma	(Liu, M.*et al.,* 2011)[35]	Mix 100 µl of sample in 3% of formic acid with Acetonitrile solvent Solvent Volume: (200 µl) Vortex time: 30 sec	Method: Liquid Chromatography- Electrospray Ionization

			Centrifugation time: 10min Centrifugation temperature: 4°C Evaporation: nitrogen stream Evaporation temperature: 40°C Solubilization process: 100 µl with (20% methanol)	Mass Spectroscopy HPLC Column used: Capcell Pakc18 (MG, 100 × 2.1mm and 5µm) Mobile Phases: formic acid methanol Ratio: (60:40 v/v) Temperature: 25°C Flow rate: 0.4 ml/min Method- Mass Spectroscopy detection process Source: Electro-spray Ionization Quantification mode: MRM
15	Rat plasma Rat tissue	(Wang, Z.*et al.,*2016)[36]	Method- Rat plasma process Solvent used: methanol Mixing ratio: 200 µl with standard 40 µl and 560 µl solvent. Vortex at: 20 sec Centrifugation time: 10min rpm: 12000 Filtration process: Rat tissue Grinding process: 3ml saline solution with 600 mg tissue Centrifugation time: 10min rpm: 12000 Mixing ratio: 200 µl with standard 40 µl in 560 µl Vortex at: 20 sec Centrifugation time: 10min rpm: 12000	Method: Ultra Performance Liquid Chromatography (UPLC) or Mass Spectroscopy process Column used: Acquity Ethylene bridged hybrid (C18, 50 × 2.1mm and1.7µm) Mobile Phase used: acetonitrile formic acid and water Ratio: (0.1:99.9, v/v) Flow rate: 0.25 ml/min **Mass Spectroscopy detection:** Source of detection: Electro-spray Ionization Quantification by: different Reaction Monitoring mode
16	Rat plasma	(Xu, B.*et al.,* 2015)[37]	Evaporation of the 10 µl IS with working tube Mixing ratio: 200 µl with internal evaporated solution Vortex time: 1min Mixing ratio: 10 µl with1% formic acid or 200 µl acetone Vortex time: 2min Centrifugation time: 10min, rpm: 10.000 rpm Mixing ratio: supernatant by 200 µl methanol Vortex time: 1 min centrifugation time: 10 min Mixing ratio: supernatant by 400 µl acetonitrile Vortex time: 1 min centrifugation time: 10 min	Method: Liquid Chromatography Mass Spectroscopy Column used: Zorbax Eclipse eXlta Dense Bonding (C18, 150 × 2.1mm and 3.5µm) Mobile Phase used: acetonitrile and water Ratio: 1% acetic acid and 0.001 mol/L ammonium acetate Flow rate: 0.2 ml/min **MS detection:** Source: Electro-spray Ionization Quantification by: Multiple Reactive Monitoring mode

			Dryness: Nitrogen stream Temperature: 37°C Resolubilize with methanol	
17	Rat plasma	(Yang, L.*et al.,*2017)[38]	Solvent used: Methanol Mixture: 100 µl sample with internal standard of 10 µl Centrifugation time: 10 min rpm: 12.000 rpm Temperature: 4°C Vortex time-1min Evaporation: nitrogen stream Resolubilization with 100 µl solvent.	Method: Ultra Performance Liquid Chromatography Mass Spectroscopy Column used: Acquity **Ultra Performance Liquid Chromatography** Column used: Ethylene Bridged Hybrid (C18, 1.7µm, 50 × 2.1mm). Mobile Phase used: Acetonitrile Flow rate: 0.4 ml/min formic acid: water Ratio: (0.1:99.9 v/v) Quantification by: Multiple reactive monitoring mode MS detection: Source: Electro-spray Ionization.
18	Stem bark *Mahonia manipurensis*	(Pfoze, N.L. *et al.,* 2014)[39]	Method: Cold extraction process Solvent used: Methanol Quantity: 1000 mL Stirring: room temperature	Method- TLC Stationary phase used: pre-coated silica gel (GF-254). Mobile phase used: hexane ethyl acetate methanol Ratio: (56:20:5) Fraction and purification test: Dragendroff's Reagent (+ve test) Analysis of purified fraction: Mobile phase used: chloroform ethyl acetate diethyl-amine methanol ammonium hydroxide Ratio: (6:24:1.5:6:0.3) HPLC: Column used: Water Symmetry (C18, 250 x 4.6mm and 5µm) Mobile phase used: methanol formic acid

				buffer Ratio: (0.1%, v/v) Detection at: 346 nm Flow rate: 1 ml/min Detection by: UV spectra at 200 to 500 nm MS: Electro-spray Ionization
19	*Tinospora cordifolia*	(Satija, R.*et al.,*2015)[40]	Method: Microwave assisted extraction (MAE) process Solvent used: ethanol Time: 3 min Method: Soxhlet extraction process Solvent used: ethanol Time: 3 hr Filtration Concentration Maceration Solvents for extraction: ethanol-200ml by 7 days irregular stirring	Method: HPTLC Mobile phase used: methanol acetic acid water Ratio: (8: 1: 1 v/v/v). Detection at: 366 nm
20	*Tinospora cordifolia, Tribulus* *Terrestris, Emblica* *officinalis*	(Joshi, H.*et al.,* and Kanaki, N.*et al*., 2013)[41]	Solvent used for extraction: chloroform Sample is triturated with ammonia solution Dry: room temperature Extraction time: 1 hr phase extraction of chloroform with 5% sulfuric acid Basic nature: by acid extract with sodium carbonate pH: 9 Extraction with chloroform: X3 Evaporation temperature: 50°C Residue solubilized by methanol	UV absorbance at: 348 nm (wavelength)

The extraction process is simple and involves several steps such as sample mixing and extraction solvents e.g. acetone, acetonitrile and methanol. Centrifugation after that the supernatant in nitrogen stream and the extraction of solid phase extraction (SPE) can be applied.

ANALYTICAL TECHNIQUES

After Berberine extraction, separation, purification and quantification use the chromatography methods. Determination of Berberine extract by using different analytic techniques such as UV-Vis spectrophotometry, High Performance Liquid Chromatography, Thin Layer Chromatography, Capillary Electrophoresis and High Performance Thin Layer Chromatography. Berberine analyzed by Liquid Chromatography-Mass Spectrophotometry, Ultra Performance Liquid Chromatography-Mass Spectrophotometry.

UV-Vis spectrophotometry

(Joshi, H.*et al.,* 2013; Kanaki, N.*et al*., 2013), they reported that they work done by this method was considered most effective and rapid detection method from Berberine extract quantitative analysis plant extracts. Berberine concentration determined by UV technique absorption at 348nm, based on Beer-Lambert Law. Done dilution range of 2-20µg/ml Berberine samples and compounds avoided by isolation of alkaloid fraction.[41]

High-performance liquid chromatography (HPLC)

(Sasidharan, S.*et al*., 2011), reported that HPLC technique widely used for quantitative analysis and qualitative analysis and also used in quantification and identification The stationary phase of C18 silica column and mobile phase used different solvents are methanol, acetonitrile and water with combination phosphate buffers. Separation and detection of Berberine compound by using isocratic gradient elution and

high sensitivity Berberine identification using UV and DAD techniques.[42]

Thin layer chromatography (TLC) and high performance thin layer chromatography (HPTLC)

(Samal, P.K.*et al*., 2013) they reported that two techniques used usually for Berberine detection by TLC method and HPTLC method. These methods were easy and cost effective. By the HPLC method present the chance of running samples at the same time use small quantity of samples as well as mobile phases. The plant *Argemone mexicana* used for the identification of Berberine by using stationary phase and mobile phase. The silica gel used as stationary phase and mobile phase used with toluene and ethyl acetate solvents.[27]

Electrochemiluminescence (ECL) end-column with CE

(Du, J.X.*et al.,* and Wang, M.*et al*., 2010) they reported that used same principles method for detection of Berberine *Rhizoma coptidis*. They developed the method to identified small volume sample and proved very sensitive with good revolution for Berberine detection.[43]

Mass spectrometry:

(Xu, B.*et al*., 2015)they reported that considered great techniques to analyzed samples. In this method, sample analyzed fast and accurate information related to the structural compounds composition in this technique. They developed accurate and sensitive methods to Berberine determine. Samples separation optimized by using six types of reverse phase columns, two mobile phases with different solvents such as methanol-water and acetonitrile-water, additives used in different concentration : 0.1, 0.5, 1, and 2% formic acetic acid and 0.0001, 0.001, 0.01 mol/L ammonium acetate, acetic acid and formic acid. The different method was tested in specificity, linearity, lower limit of quantification, stability, accuracy and precision.[37]

POTENTIAL OF BERBERINE ON THEIR THERAPEUTIC EFFECTS

Immunomodulatory potential:

Immunomodulatory effect of Berberine was established in many experimental. Berberine furnish to relieve damage in cardiac the by increasing the anti-cardiac myosin antibodies and regulate the action of some STATs or block the differentiation of Th1cytokines and Th2 cytokines cells. This route plays main function with the pathogenesis of myocarditis. Neurologic disease characterized by autoimmune damage peripheral nervous system. The useful outcome of Berberine on animal model resided in its pressure on cellular immunity and humoral immunity and the inhibition of lymphocyte proliferation (CD4) and also decrease in pro-inflammatory cytokines (IL-6 and TNF). Multiple sclerosis is a common disease of central nervous system and inflammatory processes. Berberine enhances the level of corticosteroids. We can examine the increasing level with the help of experimentally-induced colitis in rats. The benefits and the effects of Berberine may be allow and apply to the rise in level of endogenous glucocorticoid compounds with the effective and desired therapeutic action in inflammatory bowel disease.[44-46]

The various effects of Berberine are shown with their therapeutic and mechanism in Figure 2.

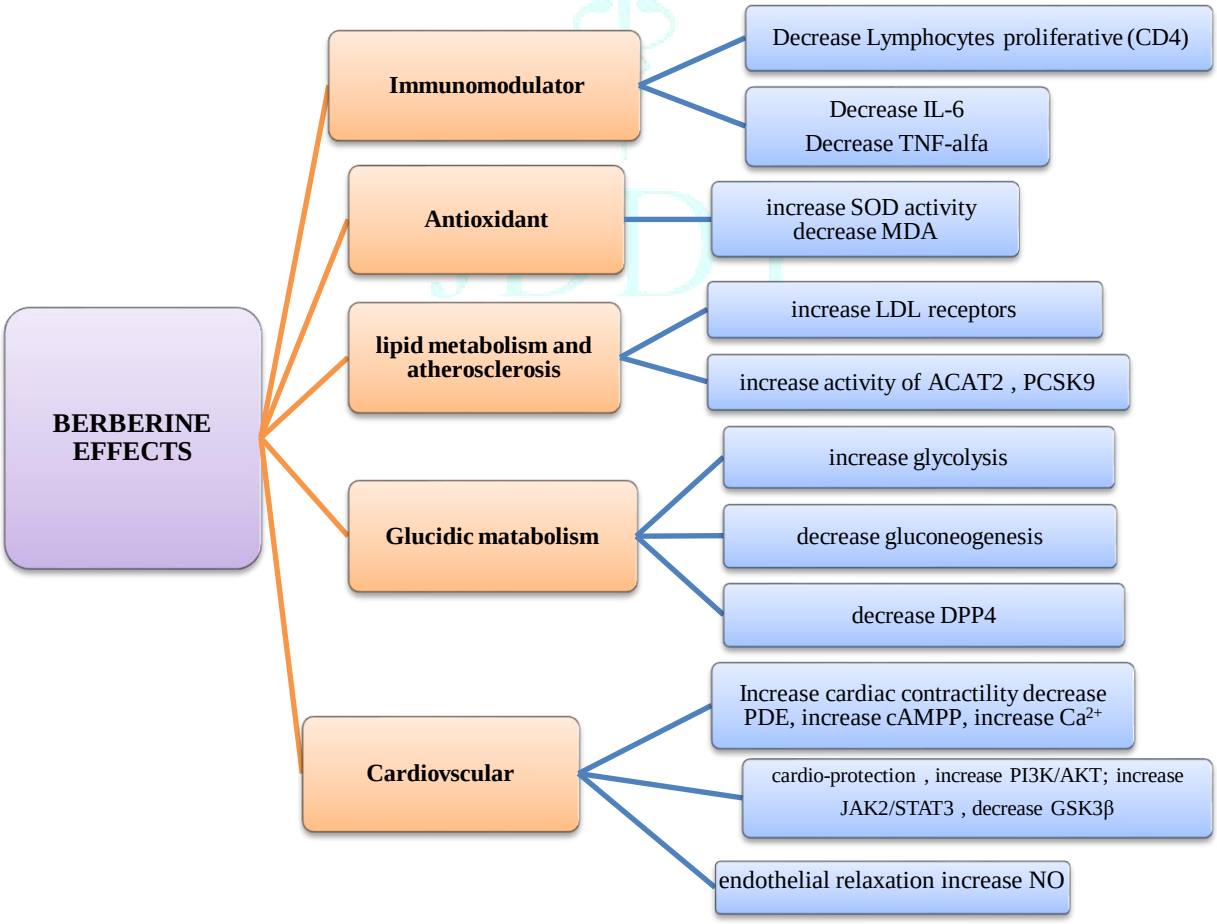

Figure 2: Potential of Berberine on their therapeutic effects and their mechanisms

Antioxidant potential:

Normal conditions body maintains balanced the antioxidant and prooxidant agents. Imbalance between pro-oxidant and antioxidant occurs high oxidative stress. Oxidative stress build several mechanisms: a production increase of reactive species, decrease enzyme levels involved in blocking actions of compounds or decrease free radical. The Berberine on peroxidation of lipids, and effect induced after chemical carcinogenesis in small animals. Berberine detects best result of antioxidant properties suitable effect on lipid peroxidation. Further, involved mechanism in antioxidant of Berberine: free oxygen removal, ROS/RNS scavenging, nitric oxide ions and reducing destructiveness of superoxide ions. Increase the antioxidant effect of endogenous substances. Highly potential antioxidant and Berberine compared with vitamin C. The oxidative stress plays a main part.[47-51]

Potential on endothelium:

Berberine induces endothelial relaxation with increasing NO production from essential amino acid through activity of endothelial nitric oxide that thought of within the dilatation method. Berberine facilitates phosphorylation of endothelial nitric oxide synthase and heat shock proteins 90, that increasing NO production. Endothelial contraction by taking Berberine and it reduced the COX-2 expression. Imbalance of the COX-1 and COX-2 activity, quantitative relation ratio between vasodilator/vasoconstrictor, and prothrombotic/antithrombotic effects. Berberine shows helpful impact on TNFa/AKT/eNOS mRNA beneficial effects.[52]

Atherosclerotic potential:

The level of blood lipid very high levels and associated with vascular wall swollen. Effect of Berberine during lipid metabolism is the significance of cholesterol low density lipoprotein receptors. Receptors stabilize by an extracellular signal regulated kinase extracellular signal regulated dependent pathway with Berberine increases the activity of low density lipoprotein receptors through JNK pathway. There are two types of enzymes; Acetyl-Coenzyme A Transferase 1 and Acetyl-Coenzyme A Transferase 2 Berberine influence on lipid profile.[53]

Hepatoprotective potential:

Berberine was established on animal studyof Berberine. Berberine reduced functional hepatic tests and histological damage (cellular infiltrate inflammation and hepatocyte necrosis). The mechanism of Berberine which reduces hepato-toxicity also considered on carbon tetrachloride (CCl_4) induced hepato-toxicity. Berberine used lowers nitrosamine oxidative stress and inflamed liver. The Berberine decreases. Berberine prevents decrease in increase in lipid peroxidation and super peroxide dismutase activity. Reduction in COX-2, TNF-αand caused nitric oxide synthase (iNOS) levels. Decrease in transaminase levels maintain. Berberine helps to maintain integrity of hepatocellular membrane.[54-56]

Potential on glucose metabolism:

Berberine low blood sugar level, and its mechanisms Inhibition mitochondrial glucose oxidation. Incentive of glycolysis and breakdown of glucose increased and decreased ATP level through inhibition of mitochondrial function in liver and gluconeogenesis. By the Berberine Inhibition of dipeptidyl peptidase-4 (DPP4), protease responsible for certain peptides such as glucagon-like peptide-1, gastric inhibitory polypeptide; rise insulin level of hyperglycemia, DPP4 inhibition. Determine peptides duration action, so improving glucose tolerance. Berberine improves the insulin resistance, and showed beneficial effects. Hypoglycemic drugs are commonly used and utilization of glucose levels in tissues with helps lowering plasma lipid free fatty acids.[57]

CONCLUSION

Herbals are the best for the used for the treatment of various diseases with lesser side effects as compared to other formulation. In this review, we came to know about the potential uses of Berberine in the various disorders and in the treatment of various diseases. With the literature, we came to know about that extraction, isolation and analysis of this plant is easy and can be done. So we can prepare the various formulations as herbal formulations for the treatment of various disorders in future.

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