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REVIEW

Berberine: A Comprehensive Review on its Isolation, Biosynthesis, Chemistry and Pharmacology

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The isoquinoline compounds from alkaloidal class have been excellent source of important phytoconstituents having wide range of pharmacological activities. Berberine is a protoberberine alkaloidal compound obtained from Berberis genus plants which belongs to family Barberidaceae. Due to its unique structural properties, berberine and its derivatives has been exploited extensively for its potential uses in various pharmacological targets such as cancer, inflammation, diabetes, gastrointestinal disorder, viral and microbial infections, neurological disorder like Alzheimer, anxiety, schizophrenia, depression, *etc*. This review illustrates the updated information on berberine with respect to its isolation, biosynthesis, chemical synthesis, structural modification and pharmacological activities. An extensive literature search were carried out in various search engine like PubMed, Google Scholars, Research Gate and SCOPUS by using keywords like Berberine, protoberberine alkaloids, isoquinoline derivatives, pharmacological effects, *etc*. Prephenic acid is the starting material for biosynthesis of berberine. Structural modifications lead to generation of various potential derivatives, which earn patents by researchers. Besides toxicities, the complications of low solubility and bioavailability should be eliminated. To improve its safety, efficacy and selectivity the berberine should be carefully derivatized.

Keywords: Berberine, Isoquinoline alkaloid, Biosynthesis, Chemistry, Pharmacology.

INTRODUCTION

Nature is a great source of secondary metabolites which exhibits huge potential to cure and mitigate various disease and ailments with negligible side effects. Peoples were using these kinds of plant material from time immemorial [1]. Among so many therapeutically important plants, the species of Barberidaceae family are of special significance because of its wide range of traditional as well as modern clinical uses, mainly due to the presence of potent bioactive compound, berberine (Fig. 1).

The name 'berberine' (**1**) was given by Buchner & Herberger [2] for a yellow extract obtained from the *Berberis vulgaris* in 1830. The molecular formula of berberine is $C_{29}H_{19}NO_4$ and molar mass is 337.37 g/mol, which were confirmed by various analytical methods. The IUPAC nomenclature of berberine is 9,10-dimethoxy-5,6-dihydro[1,3]dioxolo[4,5-*g*]isoquinolino[3,2-*a*]isoquinolin-7-ium chloride. Berberine is an alkaloid belongs to isoquinoline class, which is mainly found in roots, rhizomes and the stem barks of medicinal plants like *Berberis aristata* (tree turmeric), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (Barberry), *Coptis chienesis* (coptis or golden thread) and *hydrastis Canadensis* [3-5]. It is bright yellow in colour and show strong yellow fluorescence when viewed under UV light [6]. Berberine can be synthesized chemically and for clinical purpose the sulphate or chloride salts of berberine are mostly preferred. The powder of berberine possess intense yellow colour, odourless and bitter in taste. It is slightly

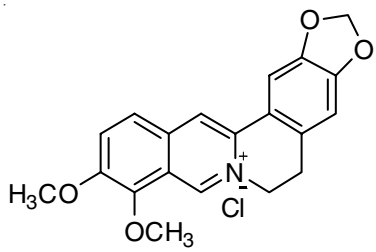


Fig. 1. Structure of berberine (**1**)

soluble in water and ethanol whereas salt form are readily soluble in common solvents [7]. Berberine has been used in Ayurvedic and Chinese system of medicines for more than 3000 years for its antiprotozoal, antimicrobial, and antidiarrheal properties [8]. In India, it can be easily found in Himalayan region and Nilgiri hills [9]. Most active constituents include berberine, berbamine and palmatine [10]. Studies revealed that berberine possess several pharmacological activities such as antihypertensive, antihyperglycemic, antiarrhythmic, anticancer, antidepressant, anxiolytics, neuroprotective, antioxidant, anti-inflammatory, analgesics, *etc*. [7,11,12].

Natural source of barberine: Berberine is widely present in various plant families and genera including Annonaceae (*Annickia*, *Coelocline*, *Rollinia* and *Xylopia*), Berberdaceae (*Berberis*, *Caulophyllum*, *Jeffersonia*, *Mahonia*, *Nandina* and *Sinopodophyllum*), Menispermaceae (*Tinospora*), Papaveraceae (*Argemone*, *Bocconia*, *Chelidonium*, *Corydalis*, *Papaver* and *Sangunaria*), Ranunculaceae (*Coptis*, *Hydrastis* and *Xanthorhiza*) and Rutaceae (*Evodia*, *Phellodendron* and *Zanthoxyllum*) [13]. Among all these genera, berberine is extensively distributed in the genus *Barberis,* where the bark of *Barberis vulgaris* contain 8% alkaloids and out of this, 5% of its total constituents is berberine [14].

Literature revealed that the berberine is widely present in bark, twigs, leaves, rhizomes, roots and stems of various medicinal plants such as *A. mexicana*, *B. aristata*, *B. aquifolium*, *B. heterophylla*, *P. amurense*, *P. chinense*, *T. cordifolia*, *etc*. [15-20]. *Chelidonium majus* is a medicinally important plant from papaveraceae family where berberine is found in maximum extent [21]. Various group of researchers revealed that, higher concentration of berberine present in roots (1.6-4.3%) and low altitude plants bearing higher amount of berberine than higher altitude one [22]. The concentration of berberine also depend on season and timing of harvesting, for example maximum amount of berberine can be obtained from *B. pseudumbellata* in summer season where its concentration is 2.8% in roots and 1.8% in stems as compared to 1.9% in roots of *B. aristate* when harvest in winter [23].

Extraction: Berberine is a quaternary protoberberine alkaloid (QPA) and it can be isolated from their matrix by several methods. The basic mechanism behind the extraction is interconversion reaction of protoberberine salt and base because salts are easily soluble in water, stable in acidic and neutral media whereas organic solvents are used to solubilize the base [2,24]. Most commonly used extraction methods are maceration, Soxhletion, percolation, hot or cold extraction by using various solvent system like ethanol, methanol, chloroform, aqueous or acidified mixtures and maintaining of temperature is considered as most crucial factors [25]. The solvents need to be acidified by adding 0.5% organic or inorganic acids so that acidified solvents can form salt with free base in plant extracts where 0.34% phosphoric acid was considered to be optimal for extraction [26]. Apart from conventional method of extraction, nowadays several advance extraction methods are being used such as ultrasound assisted solvent extraction (USE), microwave-assisted solvent extraction (MAE), ultrahigh pressure extraction (UPE), pressurized liquid extraction (PLE). This kind of extraction methods are reported to be more efficient, green, simple and inexpensive in nature.

A simple extraction method of berberine was described by Marek *et al*. [24]. Berberis plant (roots) collected, remove dirt and stone and then cut into small pieces by using filament cutter. Crude drug was poured into fermentation vat and soaked for 24-36 h with 0.1-1% aqueous sulfuric acid and repeat the process for 3-5 times by successive addition of H_2SO_4 and finally with water. Soaked solution was filtered and neutralized by adding milk of lime to maintain pH of 7-9. Conc. HCl was added for formation of berberine salt as yellow crystal and crystal were filtered with filter sieve and berberine hydrochloride was isolated (Fig. 2).

Biosynthesis: The biosynthetic pathway of berberine from *Hydrastis canadensis* was investigated by using radioactive markers such as radioactive phenylalanine, glucose, tyrosine and dopamine. Earlier, a classical hypothesis was given by Trier & Winterstein [27], which was elaborated by Robinson [28] and finally advanced and extended by Robinson and others [29]. Wenkert's hypothesis on the biosynthesis of aromatic amino acid from prephenic acid (**2**) precursor is given in Fig. 3 [29]. Dopamine (**3**) synthesized from prephenic acid, then treated by formaldehyde and further react with 3-(3,4-dihydroxyphenyl)-2-oxopropanoic acid (**4**) to form berberine (**1**) [30].

Various researchers revealed that there are several pathways exist for biosynthesis of protoberberine alkaloids [31,32]. (*S*)-Reticuline (**5**) is the central intermediate for biosynthesis of tetrahydroisoquinoline alkaloid derivatives which is obtained by reacting substrate dopamine (**3**) and *p*-hydroxyphenyl acetaldehyde (**6**). Both the reactants are coupled by norcoclaurine synthase to form (*S*)-norcoclaurine (**7**) and then *S*-adenosyl methionine (SAM)-dependent-O-methyl transferase methylate one hydroxyl group to form (*S*)-coclaurine (**8**). Further, (*S*)-coclaurine (**8**) is catalyzed by enzymes such as SAM-dependent *N*-methyl transferase and heme-dependent hydroxylase to form (*S*)-reticuline (**9**) (Fig. 4) [33].

Then, (*S*)-*s*coulerine (**10**) was formed from (*S*)-reticuline (**9**) by the action of flavin dependent berberine bridge enzyme. Methylation of (*S*)-*s*coulerine (**10**) carried out by scoulerine 9-O-methyltransferase to yield (*S*)-tetrahydrocolumbamine (**11**), which was further converted to (*S*)-canadine (**12**) and finally, catalyzed by tetrahydroprotoberberine oxidase to form berberine (**1**) (Fig. 5) [34].

Chemical synthesis: In chemistry of natural products, the isoquinoline skeleton is the most important core structure of alkaloids class. Gatland *et al*. [35] worked on short and efficient synthesis of protoberberine by using palladium-catalyzed enolate arylation. Synthesis started with methylation and acetal protection of benzaldehyde (**13**) for synthesis of aryl bromide (**14**). Compound (**15**), which act as the coupling agent was synthesized from commercial acid (**16**) by reduction, free alcohol protection as pivaloate ester and Friedel-craft acylation. Product (**17**) was formed by coupling of compounds (**14** and**15**) through α-arylationin presence of Cs_2CO_3 and 5% mol [$(Amphos)_2PdCl_2$]. Hydrolysis and aromatization were carried out on product (**17**) by using NH_4Cl and $EtOH/H_2O$ to

Fig. 2. Flow chart of extraction of berberine hydrochloride

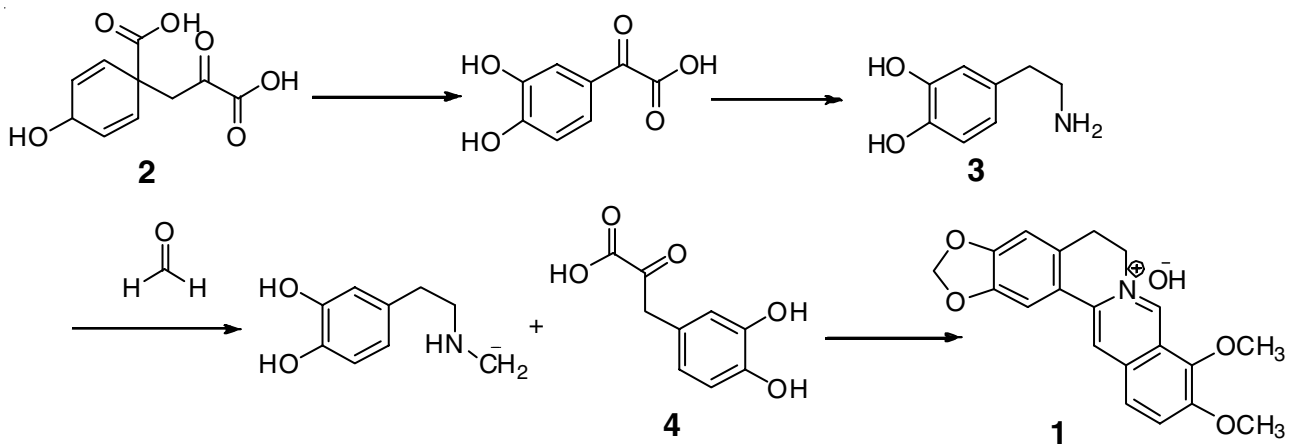


Fig. 3. Biosynthesis of berberine by using prephenic acid hypothesis

form desired isoquinoline intermediate (**18**) in which characteristics yellow colour crystal of berberine was formed by partial displacement of pivaloate by nitrogen of isoquinoline (Fig. 6). On the other hand, compounds (**14** and **15**) can be converted to berberine by using one pot synthesis method in presence of 5% mol [$(Amphos)_2PdCl_2$], Cs_2CO_3, tetrahydrofuran, NH_4Cl and $EtOH/H_2O$ and temperature of 90-110 ºC [35].

Structural modification and derivatives

Derivatives used against cancer: Berberine, a highly potential molecule, which is having a vast number of pharmacological activities including anticancer properties because of capability to damage DNA or RNA through strong complex formation by positively charged nitrogen atom on C-7 position

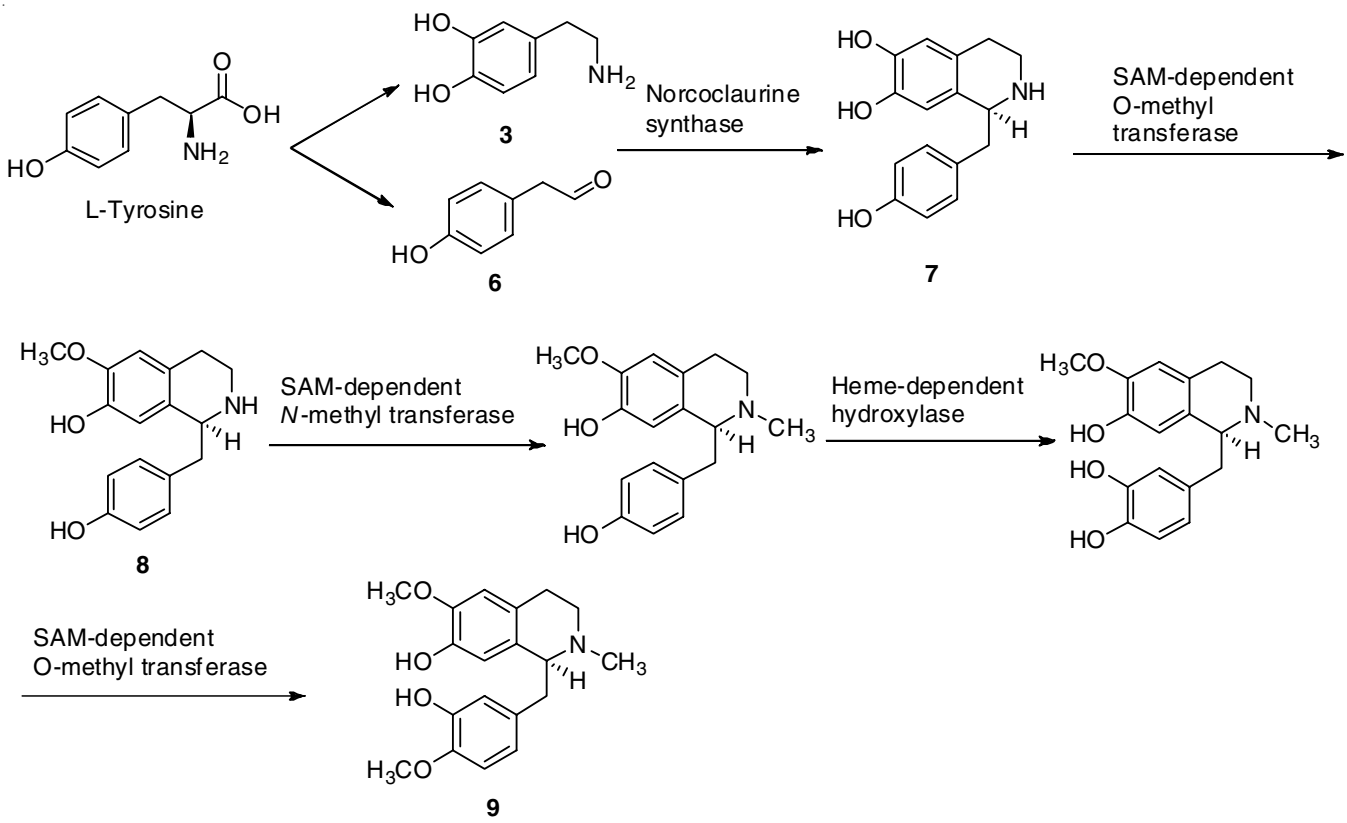


Fig. 4. Biosynthesis of (*S*)-reticuline

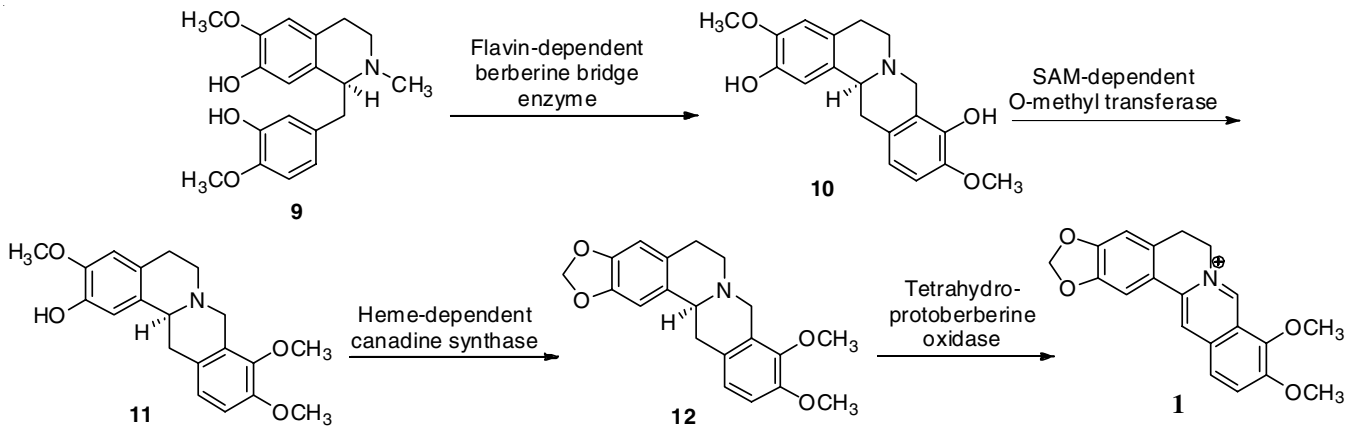


Fig. 5. Biosynthesis of berberine from (*S*)-reticuline

of berberine [36-39]. Moreover, diverse modification on the structure of berberine can generate very useful molecules with different pharmacological activities. The growth of transplanted sarcoma strain 180 can be inhibited by semi-synthetic derivatives such as 9-dimethyl-9-cinnamoylberberine chloride (**19**),13-methylberberrubine cinnamoate chloride (**20**) and 13-methylberberrubine acetate chloride (**21**) [40]. Compound 8-(diethylmalonate)berberine (**22**) showed highly cytotoxic activity against pancreas cancer cell line PANC-1 and mild antiproliferative activity against leukemia cell line K562 whereas 8-propyldican berberine (**23**) show relatively less toxic against K562 [41]. ^{18}F-labelled berberine was injected in rabbit with VX2 muscle tumor and found that labelled compound was distributed between tumor and contralateral muscle [42]. Ortiz *et al.* [43] investigated four derivatives of berberine (**24-27**) against HCT116 and SW613-B3 cell line of colon carcinoma and found that all the four compounds have significant ability to reduce cell number, inhibit viability of cells and induce apoptosis.Compounds (**28-30**) were evaluated in tumor cell lines such as HepG2, Bel-7402 and HCT1 and all the comp-ounds were exhibited very good cytotoxic properties against tumor cell lines [44]. A combination of alkaloids from *Chelido-nium majus* and semi-synthetic derivatives of thiophosphoric acid compound named as Ukrain (NSC-631570) (**31**) showed anticancer properties in terminal stage and this drug is under Phase II clinical trials.

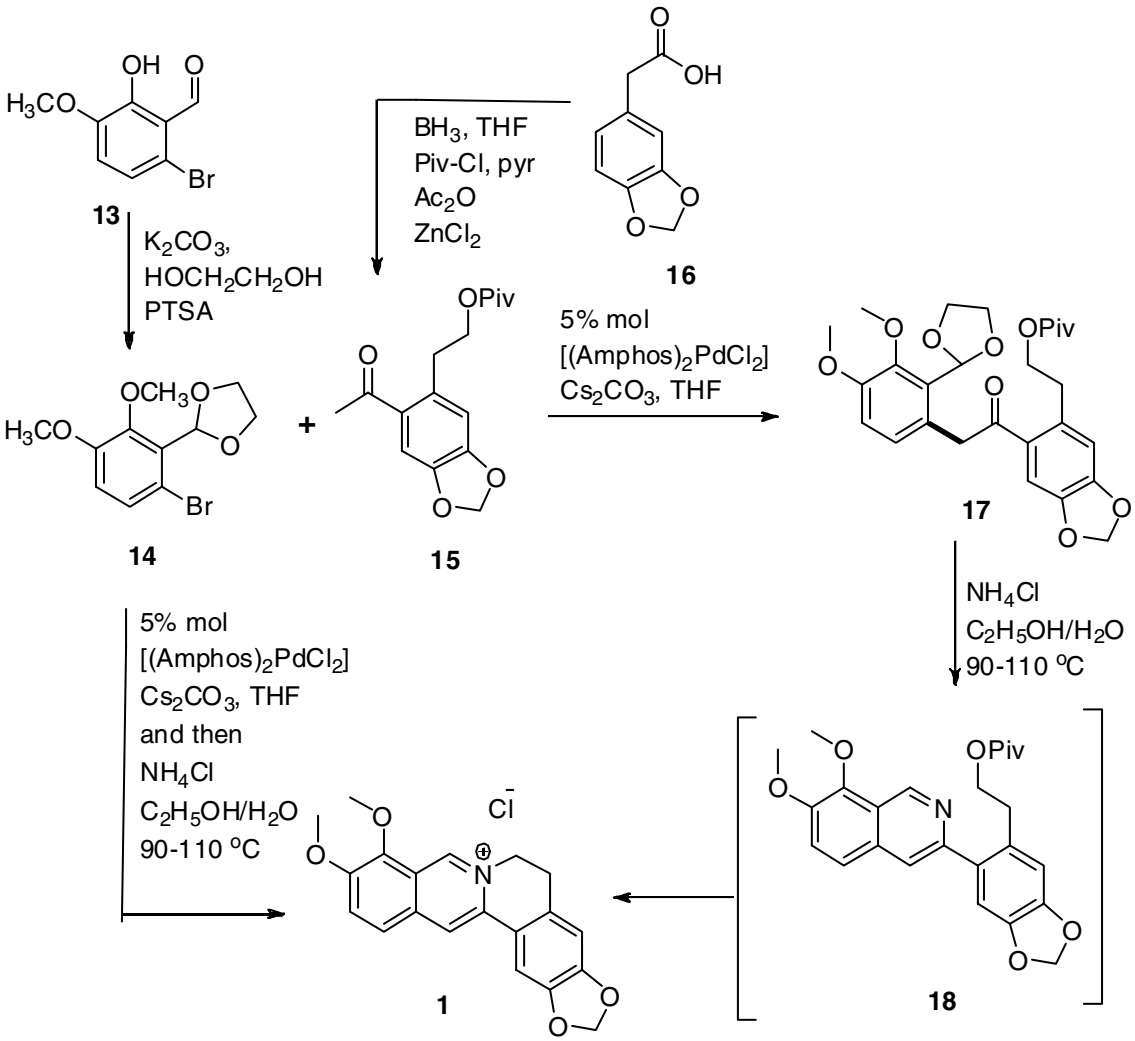


Fig. 6. Chemical synthesis of berberine. Piv= Pivaloyl, PTSA = *para*-toluenesulfonic acid, pyr = pyridine, THF = tetrahydrofuran

Derivatives used against diabetes mellitus: Antidiabetic property was exhibited by compound 12-aminomethyl berberrubine (**32**) was evaluated against type 2 diabetes mellitus in 3T3-L1 adipocyte and L6 myotubes and found that compound (**32**) show significant antidiabetic property like metformin and α-glucosidase inhibiting property was exhibited by compound 2,3,4-trihydroxybenzaldehyde-9′-O-berberine acylhydrazone (**33**) [45]. Polynuclear compound (**34**), which contain berberrubine-magnolol dimer having property of promoting glucose metabolism and can be used against diabetes mellitus. Available literature revealed that high dose of aspirin can inhibit glucose production, increase insulin sensitivity and decrease rate of clearance of insulin through IKKβ pathway [46]. Therefore, compound berberine-acetylsalicylic acid salt (**35**) can be used in tablet formulation for treatment of type II diabetes. As mangiferin have the property to reduce blood glucose level and induce carbohydrate metabolism, therefore berberine-mangiferin salt (**36**) was evaluated against streptozotocin induced diabetes mellitus and it shows desired activity after evaluation [26]. A series novel carbohydrate modified berberine derivatives were designed, synthesized and evaluated against HepG2 cell lines for antidiabetic property, among them berberine modified with mannose compound (**37**) showed high antidiabetic activity with lower cytotoxicity and higher stability under acidic conditions [47].

Derivatives used against inflammation: It is reported that berberine can reduce inflammation in adipose tissue and intestine of various human and animal tissues [44,48]. It has been found that patient treated with berberine showed inhibitory activity on cyclooxygenase-2 (COX-2), prostaglandins synthesis, tumor necrosis factor-α (TNF-α) through activation of AMPK in macrophage [49]. If a patient treated with berberine derivative for anti-inflammatory activity, there is a maximum chance that it will be beneficial for the treatment of metabolic disorder too [50]. Two compounds (**38** and **39**), which contain glycyrrhetinate enantiomeric salt of berberine was evaluated and both compounds exhibit anti-inflammatory activity [51].

Derivatives used against atherosclerosis: Some studies have also revealed that berberine has serum cholesterol level lowering properties in LDL receptors of hepatic cells of humans [52,53]. ApoE induced atherosclerosis mice were treated with compound dihydroberberine (**40**) and 8,8-dimethyldihydroberberine (**41**) and found that both compounds can inhibit reduce atherosclerosis significantly [54].

Derivatives used against anti-myocardial ischemia: Some of the quaternary ammonium protoberberines such as 13-methylcolumbanine (**42**), columbamine (**43**), 13-methyldehydrocorydalmine (**44**), palmatine (**45**) and dehydrocorydaline (**46**) were isolated from *Corydalis yanhusuo* were showed anti-myocardial ischemia effects by targets VEGF-triggered ERK1/2 pathways [55].

Pharmacological activities: Due to the alkaloidal nature, berberine possesses variety of pharmacological activities such as anti-hypertensive, anti-inflammatory, antidiabetic, hypolipidemic, antioxidant, antidepressant, antimicrobial, anticancer and antidiarrheal. Berberine has also been used in the treatment of trachoma, oriental sore, hypercholesterolemia, gastric problem, congestive heart failure and in neurological problem [56].

Anti-diabetic activity: Berberine possesses antidiabetic properties in *in- vivo* animal models and also in human clinical trials [57-62]. In hepatocytes, berberine possesses glucose-lowering effect by protecting liver cells from ER stress [63]. Through its agonistic action on the fatty acid receptor GPR40, berberine regulates insulin secretion from beta cells [64]. In many *in vivo* and *in vitro* studies treatment with berberine showed increased in AMPK activity in L6 myotubes and 3T3-L1 adipocytes. Due to which, it decreased accumulation of lipid in 3T3-L1 adipocytes and increased translocation of GLUT4 in L6 cells, which is effective in the treatment of diabetes as well as obesity [65,66]. In a dose-dependent manner berberine stimulate the expression of insulin receptors mainly in liver, through upregulation of insulin receptor mRNA [67,68]. Berberine has also been found useful in the maintaining post-receptor signal transduction [63]. Liu *et al.* [69] in their studies showed that berberine possesses a therapeutic effect on fat-induced hepatic insulin resistance (FIHIR) in a type 2 diabetic hamsters model by regulating the hepatic liver X receptor α (LXRα), sterol regulatory element binding protein (SREBPs) and peroxisome proliferator-activated receptor α (PPARα) transcriptional pathways. Due to its low bioavailability and poor absorption, berberine may possess its anti-hyperglycaemic activity in the intestinal tract before reaching to other part of the body such as pancreas or liver [3].

Hypolipidemic activity: Berberine possesses significant lipid-lowering activities [70]. Nan *et al.* [71] showed that berberine upregulated the low-density lipoprotein receptor (LDLR) in liver in an *in-vivo* rat model. Abidi *et al.* [72] also showed that the extract of goldenseal, which contains berberine and other alkaloids, reduced the LDL- cholesterol level in blood and increased the LDLR in a hamster model. Galvez *et al*. [56] suggested that the lipid-lowering effect of berberine is mainly due to its ability to increase bile formation and secretion. Through its hydrophobic and hydrophilic binding sites, berberine have the ability to interact with micelles and form alkaloid-bile salt agglomerates, which decreases the micelles capability to solubilize cholesterol and therefore affects cholesterol absorption [56,73]. Berberine enhanced the cholesterol lowering activity through a synergistic inhibition on cholesterol absorption when used in combination with other natural products and plant stanols [56]. Li *et al.* [74] reported that berberine promoted foam cell formation and induced development of atherosclerosis in apolipoprotein E-deficient mice model, which was found to counterbalancing the beneficial effect of the lipid-lowering property of berberine.

Cardiovascular disease: Berberine have always been beneficial in the treatment of many heart diseases such as arrhythmia, hypertension, improvement of cardiac contractile function, reduction of peripheral vascular resistance and in ischemia-induced ventricular tachyarrhythmia [75-77]. Berberine also possesses positive inotropic, negative chronotropic, vasodilator and antiatherosclerosis activities [78]. Berberine is useful in severe congestive heart failure patients and is a prominent vasorelaxant [75,79-82]. Wang *et al.* [83] reported the antiarrhythmic effect of berberine was related to suppression of delayed after depolarization in the ventricular muscle. Chun *et al.* [84] reported that berberine possesses hypotensive or vasodilatory effects. The main mechanism behind its cardiovascular effects is that berberine contributes to the blockage of ATP-sensitive potassium channels and delayed rectifier, and it stimulates Na^+-Ca^{2+} exchange pathways. Berberine also has the ability to prolong ventricular action potential duration. Berberine has some prominent effects in both the endothelium as well as in underlying smooth muscle [85]. Beside this, berberine is also engage in NO-*c*GMP pathway and angiotensin converting enzyme system or in the blockade of α1-adreno-receptor, which also contributes towards its cardiovascular effects [86-88]. Through various mechanisms such as enhance-ment of thrombolysis, thromboxane synthesis, inhibition of calcium influx and on platelets interaction with α2- adreno-receptor, berberine can hinder platelet function [3,89-91]. Zheng *et al.* [92] reported that berberine possesses the protective effect towards myocytes in an ischemia reperfusion model.

Anti-inflammatory activity: Berberine possesses some prominent anti-inflammatory properties. Because of these properties berberine can be effective in the treatment of many inflammatory disorders such as lumbago and rheumatism [93,94]. In many traditional medicine systems, to reduce body temperature, the use of berberine is mentioned [93]. The mechanism behind its anti-inflammatory activity is the capability of berberine to hinder *in-vivo* prostaglandin biosynthesis through inhibition of cyclooxygenase2 (COX2) expression and activity. By inhibiting COX2 regulatory proteins, berberine can indirectly inhibit COX2 activity [3,94,95]. Other mechanism involve in its anti-inflammatory activity is, inhibition of TNF-α, secreted from differentiating adipocytes [94]. The anti-inflammatory activity of berberine was analyzed by using *in-vivo* endotoxin-induced sepsis model. After treating with berberine, the rate of mortality and also lungs, heart damage was found to be reduced. And here the mechanism involved was related to the inhibition of phospholipase A2 activity and production of TNF-α [96-98].

Gastrointestinal disorders: Berberine is also found to be effective in gastric ulcers and other gastric problems. Pan *et al.* [99] described that berberine could effectively protect the gastric mucosa from damage in ethanol induced gastric ulcer mice model. Here berberine interfered in nitric acid production and related injury through inhibiting expression of inducible nitric oxide synthase (iNOS) and eventually speed up the

healing of ulcers in damaged gastric tissues [99,100]. Another mechanism behind its effectiveness in gastric ulcers is that berberine can improve the damage of intestinal epithelial tight junction, which is induced by pro-inflammatory cytokines and this effect is useful in the down-regulation of myosin light chain kinase pathway and nuclear factor-κB (NF-κB) [101-103]. Eaker *et al.* [102] described that berberine effectively blocked or delayed myoelectric activity and small intestine transport, which was mediated by α-adrenergic and opioid receptors and because of these properties berberine was effective against bacterial diarrhoea caused by *Escherichia coli*, *Vibrio cholera* and intestinal parasites.

Neurological disorders: Besides other effects berberine also found to be effective in many neurological disorders. Berberine is found to alter the neurotransmitters and their respective receptors inside brain. In the treatment of central nervous system related disorders such as cerebral ischemia, Alzheimer's disease, anxiety, mental depression and schizophrenia, berberine is found to be effective [104-107]. Wang *et al.* [108] in his studies suggested the neurological activity of berberine from their ability to cross blood-brain barrier and on concentration-time dependent manner they transported into the neurons.

Alzheimer's disease: Berberine possesses antioxidant, acetylcholinesterase, butyrylcholinesterase and MAO inhibition activity and reduction of cholesterol and Ab peptide level, due to which some beneficial effects in the treatment of Alzheimer's disease was noticed [109-111]. Acetylcholinesterase is important for the conversation of acetylcholine into choline. In Alzheimer's disease, the level of acetylcholine decreases inside the brain, therefore the acetylcholinesterase inhibitory activity of berberine is beneficial in combating Alzheimer's disease [111]. Zhu *et al.* [104] studied the effect of berberine in an *in-vivo* Alzheimer's disease rat model and found that after administration of berberine through intraperitoneal route, it increased the spatial memory of rat through increasing the expression of IL1β and iNOS in hippocampus. Another experiment shown that berberine can decrease the secretion of Aβ peptide by human neuroglioma cells. The aggregation and accumulation of Aβ peptide are found in the pathogenesis of Alzheimer therefore inhibition of Aβ peptide can be a good therapeutic target for the treatment of Alzheimer's disease [112,113].

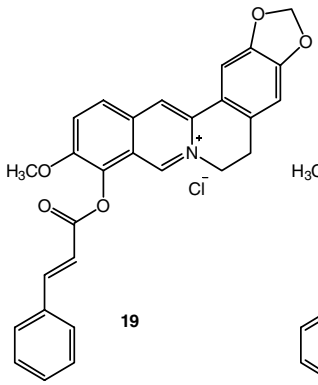
Cerebral ischemia: Berberine also possesses some beneficial effect in the treatment of cerebral ischemia. Few studies [105,114] suggested that by reducing N-methyl-D-aspartate (NMDA) receptor 1 activity and by suppressing the process of apoptosis, berberine can protect the neurons from ischemic injury in *in vivo* mice and gerbils' models. The mechanism involve behind this activity of berberine is that it can inhibit production of ROS and finally block the mitochon-drial apoptotic pathway [114]. Hong *et al.* [115] suggested that berberine can slow down the delayed hippocampal neuronal cell injury and suppressed the Matrix metalloproteinase-9 (MMP-9) activity due to which berberine shows protective effects in cerebral ischemia.

Schizophrenia: The enzyme prolyl oligopeptidase (POP) is mainly associated with schizophrenia, depression, memory loss, bipolar disorders and other neuropsychiatric disorders. POP is a cytosolic serine peptidase and is responsible for hydrolyzing proline containing peptidase at carboxy terminus [116]. In schizophrenia, the activity of POP enzyme is found to be increased [117]. Chu *et al.* [118] reported that in a dose dependent manner, berberine can inhibit the POP enzyme and also it also possesses dopamine D2 receptor antagonistic and D1 receptor agonistic activity, which may play a role in the treatment of schizophrenia.

Depression: Kulkarni & Dhir [106] suggested that berberine have an ability to inhibit monoamine oxidase-A (MAO-A) which is responsible for degradation of serotonin (5-HT) and norepine-phrine, the neurotransmitters involved in mental disorders [107]. Berberine also contributes to nitric oxide pathway and sigma receptors [100]. Nassiri *et al.* [119] reported that berberine was found to improve the neural pathway and reduced dependence of morphine and also can produce hypnosis and regulate locomotor activity.

Anxiety: Berberine also has potential anxiolytic activity [6]. Peng *et al.* [107] investigated that high doses of berberine i.e. 100, 500mg/kg have prominent anxiolytic activity. This anxiolytic effect may be due to the decrease of serotonergic activity and improvement of monoamines turnover rates in brain stem by berberine. By controlling the activity of postsynaptic 5-HT1A and 5-HT2 receptors and somatodendritic 5-HT1A auto-receptors, berberine can reduce anxiety.

Antimicrobial activity: Berberine is effective against viral, bacterial, fungal and protozoan infections [120-123]. Berberine is found to be effective against *Candida species*, *Plasmodium falciparum*, *Entamoeba histolytica*, *Giardia lamblia*, *Staphylococcus aureus*, *Trichomonas vaginalis*, *Herpes simplex*, Human immunodeficiency virus (HIV), influenza virus, human cytomegalovirus, *Chlamydia trachomatis*, *Leishmania donovani* and *Helicobacter pylori* [122-133]. In combination with multidrug resistance (MDR) pump inhibitors the antimicrobial activity of berberine increases. Ball *et al.* [134] suggested that after linking berberine with INF-55, potential inhibitor of MDR, their antimicrobial activity was found to be enhanced. The activity of berberine can be synergized by 5′-methoxyhydnocarpin, an inhibitor of MDR pump [135]. Natural compound such as chrysoplenol-D, flavones and chrysoplenetin in combination with berberine can prominently inhibits the growth of *Staphylococus aureus* [130]. Yu *et al.* [122] reproted that berberine have an ability to regain the effectiveness of β-lactam antibiotics against MDR strains *S. aureus* (MDRS). Berberine in combination with pyrimethamine is effective against chloroquine resistant malaria [136]. Berberine have the ability to inhibit sortase A and sortase B, due to which the virulence and infection potential of *Staphylococus aureus* is found to be decrease when treated with berberine [133]. By modifying the ring structure of berberine derivative one can increases the antimicrobial activity of berberine for example, replacement of methoxyl group by methylenedioxy group at different positions and by addition of lipophilic substituents with moderate sizes at the berberine ring [137,138]. In the treatment of *Staphylococus aureus* and fungal infections the alkyl-substituted analog of berberine are more effective than



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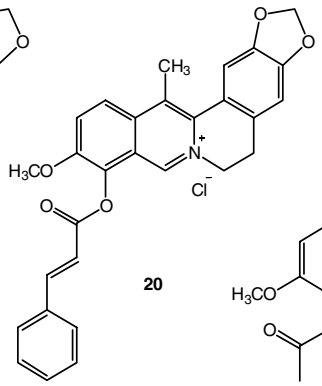

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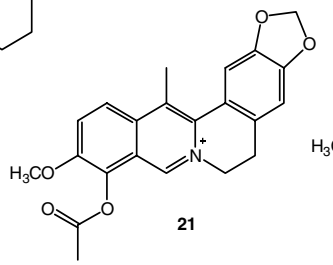

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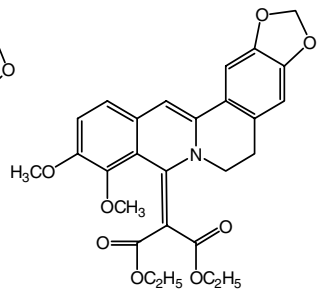

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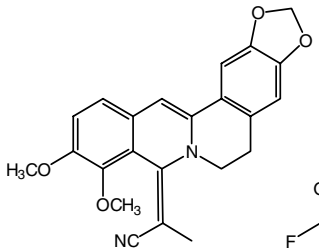

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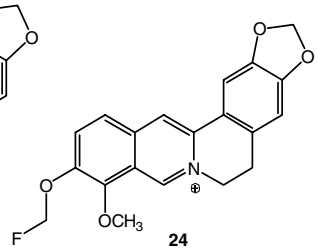

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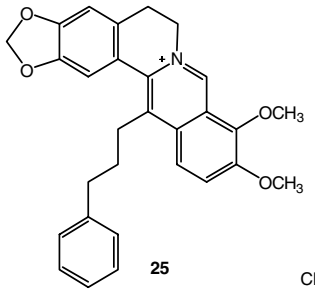

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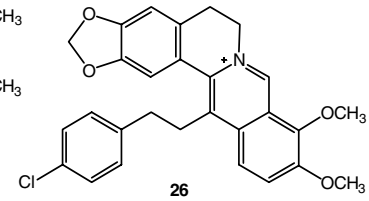

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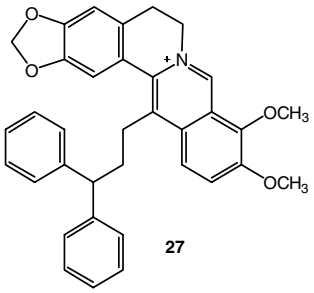

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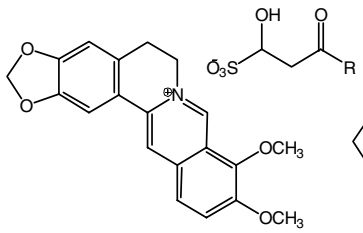

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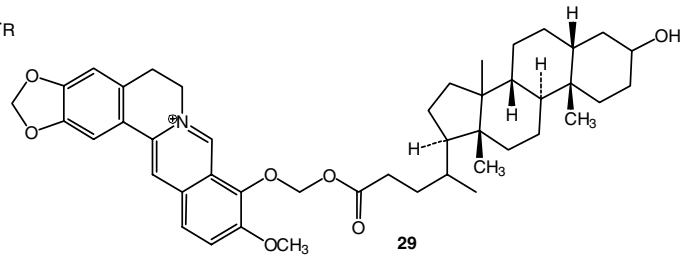

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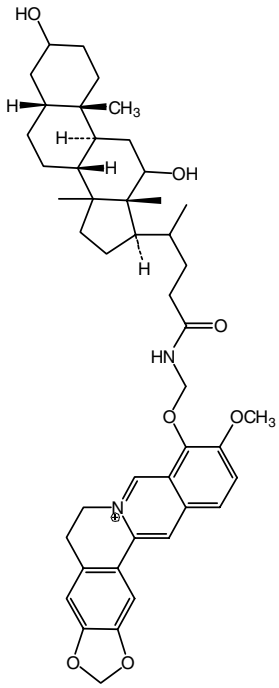

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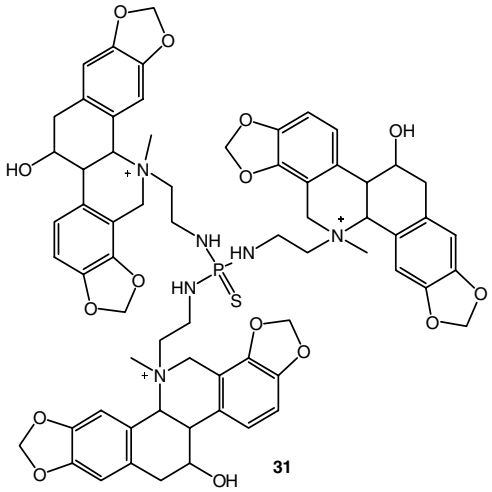

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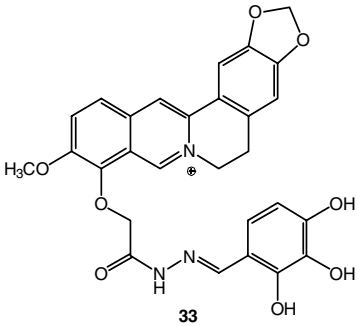

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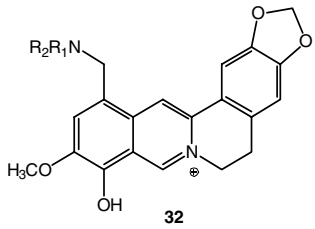

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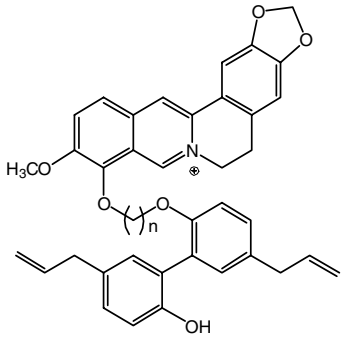

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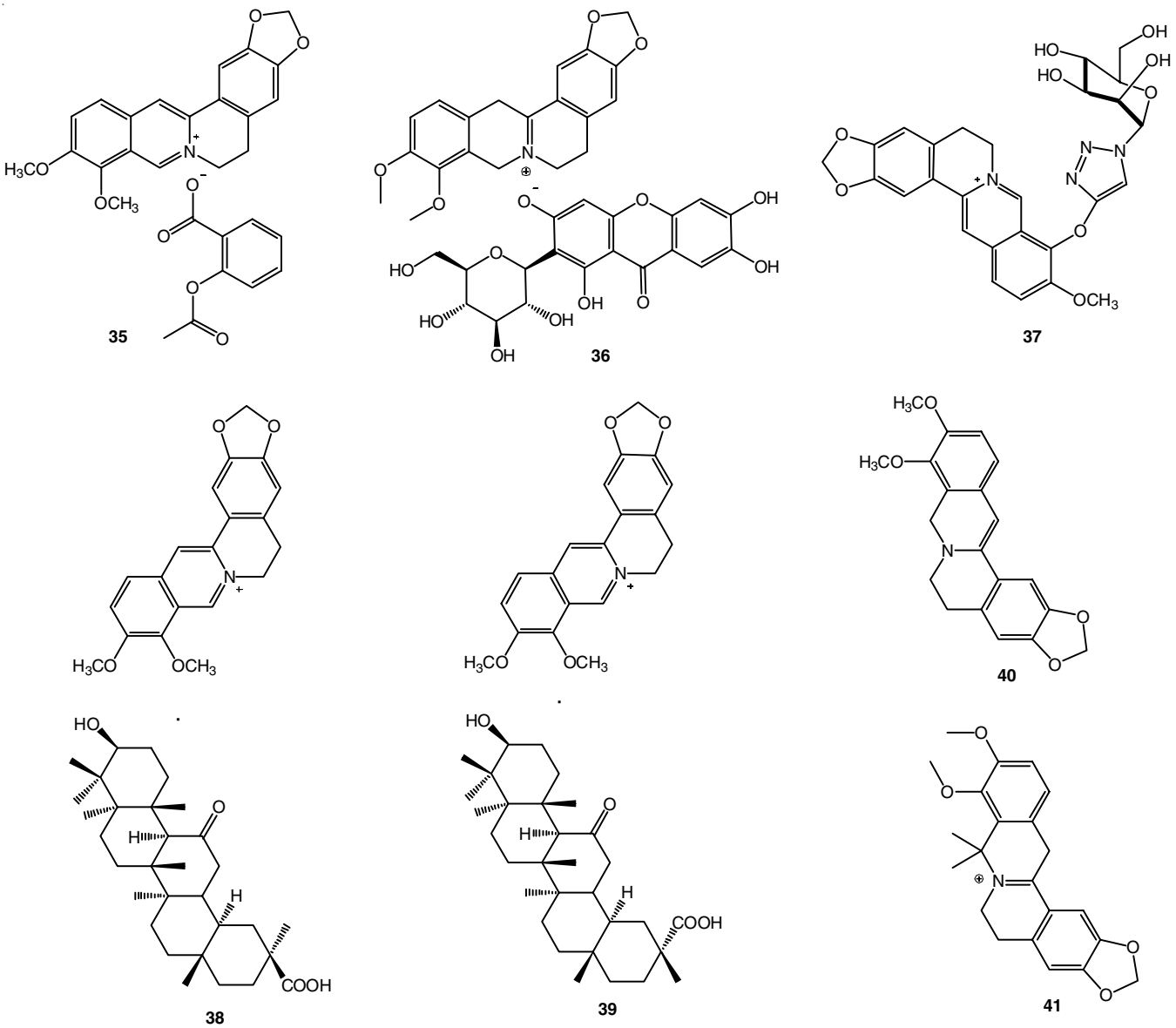

Structure of the compounds

the berberine itself [139]. Berberine is also effective in the treatment of HIV-PI induced inflammatory response in macrophages [140].

Anticancer activity: Berberine is reported to be useful against different tumour types due to its antitumoral activity [61]. Efferth *et al.* [141] from their experiment showed that IC_{50} value of berberine was similar to those other alkaloids *i.e.* vinblastine, paclitaxel, used for the treatment of cancer. Berberine is very effective in the treatment of solid carcinomas or haematological malignancies [142]. The mechanism behind its anticancer activity is that berberine can affect several steps of tumour developing such as cell proliferation, invasiveness and cell death and also it can inhibit the growth of tumour cell *in vivo* [143,144]. Berberine also has the ability to increase the effectiveness of radiotherapy or chemotherapy. Berberine has been found to activate two major proapoptotic pathways i.e. intrinsic and extrinsic pathways and can activate family of enzymes release from mitochondria such as caspases, proteases and cytochrome C, which is responsible for its anticancer activity or induction of cell death [145]. Few studies [144,146-149] suggested that apoptosis induced by berberine is initiated after damage of DNA by cell cycle arrest in G0/G1 stage, which is mediated by ATM/p53 pathway. In prostate cancer cells, cell cycle arrest in G2M, initiate by berberine is mediated through ATM/Chk1 p53-independent pathway [150]. Few studies [151,152] suggested that berberine can also induce cell death through extrinsic pathway in human hepatoma and human colon carcinoma cell lines. Berberine is also effective against liver, lung, tongue, thyroid, breast, prostate, brain, oesophageal, skin, colon, oral carcinomas [151-158]. In both tumorxeno or syngeneic transplants and carcinogen-induced tumorigenesis, berberine can prevent the development of carcinomas *in-vivo.* Berberine also has the ability to inhibit the growth of human prostate cancer cell lines and as well as human lung cancer cells [146]. Berberine can reduce the expression of androgen receptors, which is beneficial in prostate cancer [159]. Berberine

can also inhibit the growth of human tongue cancer SCC-4 cells [153]. Berberine is also effective in chemical induced carcinomas for example, it can inhibit the enhancer effect of teleocidin in skin tumours, which is induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) [160]. Berberine is also reported to be effective in acute lymphocytic leukaemia's, acute myeloid leukaemia's and some types of non-Hodgkin lymphomas [136,157,161-164].

Other activities: In the treatment of neurological conditions berberine can be used as an analgesic [157]. Berberine can also be employed in skin related infections due to its ability to suppress lipid synthesis from sebaceous glands. It can also improve skin permeability to polar drugs hence can be used as a surfactant. Other than these it also possesses antioxidant, renal protective, hepatoprotective, anti-platelet, anti-hypertensive activities [61].

Toxicity of berberine: Kulkarni *et al.* [165] from their experiment provides some toxicity data of berberine. According to their published data, oral administration of berberine (100mg/kg) initiate vomiting and after same dose for 8-10 days caused death of all animals. Also, oral administration of 50/100 mg/kg of berberine sulphate for 10 days caused haemorrhagic symptoms in cats. Some mild adverse effects of berberine is salivation, diarrhoea, nausea, emesis, paralysis and muscular tremor [166]. Sub-acute toxicity of berberine includes increase in body weight, gastric ulcers, Freund's complete adjuvant-induced chronic arthritis, bilirubin protein binding decreases, enlargement of kidney and liver [93,167]. Some immune-toxic effects of berberine *i.e.* suppression of both humoral and cellular immune functions was reported by Mahmoudi *et al.* [168]. They reported that 10 mg/kg dose of berberine decreased the leukocytes, lymphocytes, neutrophils numbers and spleen weight. Berberine also decreased the B and T cells, splenic CD4+ and CD8+ T-cells and CD19+ B-cells [168]. By increasing alanine aminotransferase (ALT) and aspartate aminotransferase (AST) berberine found to be a cause of liver and kidney damage [169]. Intraperitonial (I.P) treatment of berberine (5 mg/kg) for 15 weeks found to initiate atherosclerosis, uterine contraction and may also produce teratogenic effects [74].

Conclusion

Berberine is a protoberberine alkaloidal compound with multifunctional properties. It has been extensively isolated from plant belong to Barberidaceae family. Berberine is biosynthesized through prephenic acid pathway and reticuline acts as a central intermediate. It can also be synthesized through chemical pathways by taking benzaldehyde as a starting material. Due to presence of quaternary nitrogen atom in its structure, it exhibits various pharmacological activities such as anticancer, antidiabetic, antimicrobial along with potential to mitigate certain neurological disorders as well. By structural modification, various therapeutically important derivatives are being obtained and simultaneously used against certain diseases and metabolic disorders. Although berberine has lots of beneficial effects but it is not devoid of its toxicity. By identifying the parameters responsible for its toxicity, certain modification or elimination of those parameters can make these molecules less toxic. Along with toxicities, the complications of low solubility and bioavailability should also be handled by preparing suitable dosage forms. To improve its safety, efficacy and selectivity the berberine should be carefully derivatized.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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