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Pharmacological and analytical aspects of bergenin: a concise report

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ABSTRACT

Bergenin is a C-glucoside of 4-O-methyl gallic acid found in the form of colourless crystalline compound. It is isolated from different plants such as *Bergenial crassifolia* (*B. crassifolia*), *Corylopsis spicata* (*C. spicata*), *Caesalpinia digyna* (*C. digyna*), *Mallotus japonicus* (*M. japonicus*) and *Sacoglottis gabonensis* (*S. gabonensis*) *etc*. Isolation and characterization of bergenin were confirmed through different spectroscopic methods. Bergenin exhibits antihepatotoxic, antiulcerogenic, anti-HIV, antifungal, hepatoprotective, antiarrhythmic, neuroprotective, anti-inflammatory, immunomodulatory and burn wound healing properties. Though different methods have been developed for isolation and characterization of bergenin in different sources, still liquid chromatography and ultraviolet spectrophotometry is most commonly used techniques. Present review described the pharmacological activity, analytical methods and isolation techniques of bergenin, which give an idea about the nature and activity of bergenin. This review could be helpful to the researcherers in the future for the development of new drugs for the treatment of various types of illness. The data in the present review were collected from the available literature sources.

1. Introduction

Bergenin is a C-glucoside of 4-O-methyl gallic acid is a colourless crystalline polyphenol isolated from medicinal plants like *Bergenial crassifolia* (*B. crassifolia*), *Mallotus philippinensis* (*M. philippinensis*), *Corylopsis spicata* (*C. spicata*), *Caesalpinia digyna* (*C. digyna*), *Mallotus japonicus* (*M. japonicus*), *Sacoglottis gabonensis* (*S. gabonensis*) *etc*. It is hydrolyzable tannin and an isocoumarin derivative with three hydroxyl (OH) groups and two phenolic OH groups[1-4]. Bergenin containing extracts have long been used as a folk medicine in several parts of Asia. The molecular formula and the chemical structure of bergenin were confirmed by several spectroscopic methods and also by its synthesis[1]. Bergenin exhibits antihepatotoxic, antiulcerogenic, anti-HIV, antiarrhythmic, neuroprotective, anti-inflammatory and immunomodulatory properties[1]. The hepatoprotective effect of bergenin has also been reported[3]. Bergenin exhibit various biological activities such as antiulcer, antifungal, immunomodulatory and burn wound healing effects[5]. For the determination of bergenin liquid chromatography and ultraviolet spectrophotometry are mainly used[3]. Despite this extensive use, the pharmacokinetics of bergenin in human has not been studied probably because of the lack of a sensitive assay for its determination in biological fluids[6]. Berberin inhibited arachidonic acid-induced platelet aggregation more efficiently than acetylsalicylic acid and showed an antioxidative effect equivalent to that of L-ascorbic acid or quercetin[7]. In the present review data were collected from the available literature sources in regards with bergenin.

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2. Pharmacological activity

Bergenin showed a wide range of pharmacological

activities and is widely used in Traditional Chinese Medicine as well as different system of medicine. It is not used for the treatment of stomach hyperacidity, antiarrhythmic, hepatoprotective, anti-inflammatory, antitumor, anti-HIV agent as well as have neuroprotective activity[6]. Bergenin isolated from *Sciurocheirus gabonensis* showed protective action against oxidative stress. Bergenin either acts as a free radical scavenger or a redox regulatory agent. Free radical scavenging activity and antioxidant potential of bergenin on c-radiation induced liposomal lipid peroxidation, protein carbonylation and DNA (pBR322) damage were also invetigated[1]. Bergenin contains five hydroxyl groups, which play an important role in its pharmacological activity[2].

2.1. Antiinflammatory activity

Anti-inflammatory activity of bergenin was determined by the measurement of the inhibitory concentration of bergenin against COX-1, COX-2 (cyclooxygenases) and phospholipase A2 (PLA2) in *in vitro*. Bergenin did not inhibit COX-1 but selectively inhibited COX-2[8]. Bergenin and its O-demethylated derivative norbergenin prepared from bergenin are reported to show anti-arthritic activity through possible modulation of Th1/Th2 cytokine balance. Flow cytometric study showed that bergenin inhibit the production of proinflammatory Th1 cytokines (IL-2, IFN-gamma and TNF-alpha) while as potentiate anti-inflammatory Th2 cytokines (IL-4 and IL-5) in balb/c mice[9].

2.2. Antimicrobial activity

Antimicrobial activity of bergenin was evaluated against *Escherichia coli* (*E. coli*), *Salmonella enteriditis* (*S. enteriditis*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Enterococcus faecalis* (*E. faecalis*), *Staphylococcus aureus* (*S. aureus*), *Candida albicans* (*C. albicans*), *C. guilliermondii*, *Aspergillus flavus* (*A. flavus*), *A. nidulans* and *C. tropicalis*, *A. niger*, *Shigella sonnei* (*S. sonnei*), *Serratia marcenses* (*S. marcenses*) and *Klebsiella pneumoniae* (*K. pneumoniae*). Bergenin inhibit the growth of the yeasts *C. albicans*, *C. tropicalis*, and *C. guilliermondii*, but present lower activity against filamentous fungi *Aspergillus flavus* (*A. flavus*), *A. nidulans*, *A. niger*, and did not inhibit the Gram positive and Gram negative bacteria[10].

2.3. Antioxidant activity

Antioxidant activity of bergenin was investigated through beta-carotene, DPPH and a heterogeneous Fenton system and found that bergenin have antioxidant activity[11]. The antioxidant activity of bergenin isolated from *Caesalpinia digyna* (*C. digyna*) Rottler root was investigated both *in vitro* and *in vivo* models and found to have significant antioxidant potential[12]. In another study, bergenin also showed antioxidant activity in lipid peroxidation, superoxide and DPPH radical assays[13].

2.4. Cytotoxic activity

Bergenin showed antiviral activity against herpes simplex virus type-1 in non cytotoxic concentrations[14]. The cytotoxic activity of bergenin was tested against several cell lines and found to inhibit significantly[15]. Berenin was evaluated for the cytotoxic activity *in vitro*, and showed less cytotoxic activity against HepG2 cells[16]. Significant HepG2 cytotoxicity was also achieved by bergenin. Bergenin showed a tendency to accumulate cells in the G1 phase and reduced G2/M leading to apoptosis[17].

2.5. Effect of bergenin on urinary system

Bergenin was evaluated for their effects on urolithiasis induced by 3% glycolic acid in albino rats. Treatment with glycolic acid increased the urinary Ca^{2+}, oxalate and phosphorus levels, Na^{+} and Ca^{2+} excretion, and lactate dehydrogenase (LDH) activity in kidneys. Bergenin showed less significant activity in the present model system[18].

2.6. Effect of bergenin on bioavailability

Absorption characteristics of bergenin by modulation of the gastrointestinal absorption using two enhancers (borneol and Poloxamer 188, resp. F68) based on *in situ* absorption model were investigated. Both of the enhancers were able to increase the absorption percentage of bergenin. The oral bioavailability of bergenin in rats was improved in the presence of borneol or F68[19]. To increase oral bioavailability of bergenin, bergenin-phospholipid complex (BPC) was prepared. The pharmacokinetic characteristics and bioavailability of BPC were investigated after oral administration in rats in comparison to bergenin and the physical mixture (bergenin and phospholipids). The BPC is a valuable delivery system to enhance the oral absorption of bergenin[20].

3. Chemical derivative of bergenin

Radical derivatives of bergenin using .H, .OH, $.CH_3$, and $.CCl_3$ as initiator radicals were prepared based on the theoretical calculations. Frontier molecular orbital analysis showed that nucleophilic radical attack is favored on the aromatic ring. DFT thermodynamic calculations showed that the methoxyl group (O-6-CH_3) is the most favorable site for radical attack[11].

4. Physicochemical properties of bergenin

Physicochemical properties of bergenin such as solid state characteristics, solution stability, dissociation constant (pKa), solubility and octanol/water partition coefficient (Log P) were investigated. From the result it was found that bergenin was not hygroscopic and was stable against heat and humidity in the solid state, but sensitive to hydrolysis in the neutral and alkaline solution with pseudo first-order kinetics[21].

5. Isolation of bergenin

A new compound, 11-O-(4′-O-methylgalloyl)-bergenin was isolated from the MeOH extract of Crassula cv. 'Himaturi'[7]. Bergenin was isolated from the extracts of *Phyllanthus wightianus* (*P. wightianus*) through the use

of column chromatographic methods[22]. Bioassay-guided fractionation of *Astilbe rivularis* (*Astilbe rivularis*) led to the isolation of bergenin and a bergenin derivative[14]. Bergenin was isolated from the acetone extract of the stem bark of *Dryobalanops aromatica* (*D. aromatica*) by combination of vacuum and radial chromatography techniques[15]. 11-O-(3′-O-methylgalloyl)-bergenin was isolated from the rhizome of *Astilbe chinensis* (*A. chinensis*) [16]. Bergenin was isolated from arial parts of *Tridax procumbens* (*T. procumbens*)[23]. HPLC profiles of cold aqueous extract of *Ficus racemosa* (*F. racemosa*) showed the presence of bergenin while hot aqueous extract *F. racemosa* also showed to contain bergenin[24]. LC-MS analysis revealed the presence of bergenin, norbergenin, in the *Aconophora compressa* (*A. compressa*)[17]. Bergenin and 4-O-galloylbergenin was isolated from the leaves of *Mallotus philippensis* (*M. philippensis*)[25]. Caesalpinia extracts were standardized with respect to a bergenin, by LC- MS analysis[26]. Bergenin derivative, 11-0-caffeoylbergenin, were isolated from the leaves of *Securinega virosa* (*S. virosa*)[27]. The ethyl acetate and butanol extracts of the stem bark of *Peltophorum africanum* (*P. africanum*) yielded bergenin[28]. Bioassay-guided isolation and spectroscopic identification of active constituents in three *species F. racemosa* were conducted and found to contain bergenin[29]. 11-O-acetyl bergenin and bergenin was isolated by the use of column chromatographic from *Flueggea virosa* (*F. virosa*)[30]. Bergenin in the *B. crassifolia* leaves′ extracts were separated by HPTLC and identified[31]. Bioassay-guided fractionation of methanolic extractives of *Teramnus labialis* (*T. labialis*) showed the presence of bergenin as active constituents[32]. Bergenin was isolated from rhizomes of *Astilbe thunbergii* (*A. thunbergii*)[33]. Bergenin was isolated from the combined acetone and methanol extracts of roots root extractives of *Shorea robusta* (*S. robusta*)[34]. Air-dried and ground root bark of *Pentaclethra macrophylla* (*P. macrophylla*) was extracted with EtOAc, and thereafter subjected to vacuum column chromatography and from this fractions bergenin was isolated[35]. In a bioassay-directed isolation from the whole plant of *Ardisia japonica*, bergenin was obtained[36]. Bergenin were isolated and identified from the leaves of *Mallotus roxburghianus* (*M. roxburghianus*)[13]. The known compounds bergenin was isolated from the methanol extract of the roots and stem-bark of *P. africanum*[37]. A new gallic acid ester of bergenin, 11-O-(4-O-methylgalloyl) bergenin was isolated from the aerial parts of *Saxifraga melanocentra* (*S. melanocentra*) Franch[38]. Bergenin was isolated from *Sacoglottis uchi* (*S. uchi*)[11]. The extract of fruit pulp of *Endopleura uchi* (*E. uchi*) was fractionated using conventional chromatographic tecniques and bergenin was isolated from this extract[39].

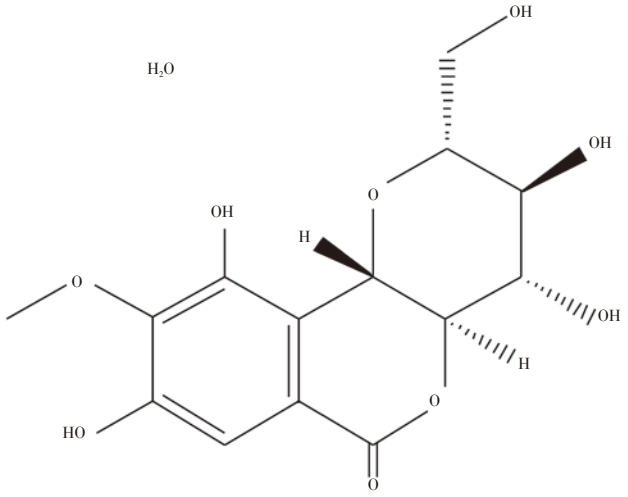

Figure 1. Structure of bergenin.

6. Analytical techniques

Content of bergenin in the Yunnan genus Rodgersia with different species and growing areas were investigated by HPLC using Agilent Zorbax XDB-C18 column, acetonitrile (A) -0.2% phosphoric acid solution as a mobile phase and flow rate of 1.0 mL/min. Bergenin content was found to be highest in *Rodgersia sambucifolia* (*R. sambucifolia*) Hemsl and the lowest in *Rodgersia aesculifolia* (*R. aesculifolia*) Batalin[40]. Two new bergenin derivatives, rivebergenin A and B were isolated from the stem of *Rivea hypocrateriformis* (*R. hypocrateriformis*)(Desr.) Choisy and characterized by ^{1}H and ^{13}C NMR spectra, DEPT, and by 2D COSY, HMQC, and HMBC experiments[41]. Analysis of bergenin in rabbit plasma by high performance liquid chromatography (HPLC) was develpoed and validated. Pharmacokinetic of bergenin was also studied in rabbits where ethyl acetate was used for extractin purpose and methanol-water (22:78) was used as the mobile phase[42]. Bergenin contents of 18 populations of *Bergenia purpurascens* (*B. purpurascens*) in Yunnan Province were analyzed by high-performance liquid chromatography (HPLC)[43]. Bergenin was isolated from the methanolic extract of the bark of *E. uchi* by liquid-liquid partition chromatography followed by column chromatography over Sephadex LH-20 and silica gel 60 flash chromatography[8]. Bergenin was isolated from ethyl acetate fraction of bark of *E. uchi* (Huber) by using column chromatography over sephadex LH-20 and then silica gel 60 flash[10]. A highly sensitive, simple and selective high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) method was developed and applied to the determination of bergenin concentration in human plasma[44]. Development and validation of an assay for quantitation of bergenin in human plasma using liquid chromatography/tandem mass spectrometry (LC-MS/MS) was investigated. Bergenin was separated by reversed phase HPLC and quantitated by MS/MS using electrospray ionization (ESI) and multiple reaction monitoring (MRM) in the negative ion mode[6]. The method for the determination of bergenin content in dicha kechuan oral liquid by high performance liquid chromatography (HPLC) was established[45]. A simple TLC method has been developed for the simultaneous quantification of bergenin using toluene: ethyl acetate: formic acid (4:6:1, v/v) as solvent system[46]. A simple, highly precise RP-HPLC method coupled with photodio-de-array detection has been developed and validated for simultaneous determination of these compounds in *B. ligulata*, *B. ciliata* and *B. stracheyi*[47]. A simple, sensitive, selective and reproducible reversed-phase high-performance liquid chromatography (HPLC)

method was developed for the determination of bergenin in rat plasma after intravenous administration[48]. An HPLC method for bergenin determination in *B. purpurascens* was established[49]. High performance liquid chromatography (HPLC) method was developed for determinating the bergenin[50]. HPLC was used and different derivatization reaction conditions were investigated for bergenin[51].

7. Discussion

From the litreature search it was found that about 25% of the drugs prescribed worldwide are derived from plants and nearly 80% of African and Asian population depends on traditional medicines for the treatment of diseases. In India, about 80% of the rural population uses medicinal herbs or indigenous systems of medicine. About 2-3 decades ago, most of the drugs were obtained from herbal source[52]. To maintain proper growth, the pharmaceutical industries needs to innovates and access to high output rate on low-cost materials with reasonable safety[52]. In the near future, bergenin will have a role that compares with that of other pharmaceutical available drugs. Bergenia species are important medicinal plants distributed in South and East Asia and European countries. In India these plants grow at high altitudes in the Himalayas usually in rocky areas and on cliffs.

Bergenia species contain most bergenin, so the most potent plant species is used in herbal formulations and has the strongest desired effect. Bergenin is a C-glucoside of 4-O-methyl gallic acid found in *B. crassifolia, C.spicata, C. digyna, M. japonicus* and *S. gabonensis etc*. Bergenin have various type of pharmacological activity such as antihepatotoxic, antiulcerogenic, anti-HIV, antifungal, hepatoprotective, antiarrhythmic, neuroprotective, anti-inflammatory and immunomodulatory activity. Several analytical methods have been developed so far the determination of bergenin in plant extract as well as in biological system. In this review we have collected the data regarding the pharmacological activity, analytical methods and isolation technique of bergenin, and combined into a paper which can be helpful researchers to give an idea about the nature and activity of bergenin which might be used in the future for the development of new drugs for the treatment of various type of ilness.

Conflict of interest statement

We declare that we have no conflict of interest.

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