Pharmacognosy Reviews [Phcog Rev.]
Vol 2, Issue 4, Jul-Dec, 2008
Page 392-401

PHCOG REV.
An official Publication of Phcog.Net

PHCOG REV.: Plant Review
The Genus *Bryonia* : A Review

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ABSTRACT

The review includes 103 references on the genus *Bryonia*, and comprises ethnopharmacology, morphology and microscopy, phytoconstituents, pharmacological reports, clinical studies and toxicology of the prominent species of *Bryonia*. Alkaloids, flavonoids and triterpenoids constitute major classes of phytoconstituents of the genus. A few species of this genus have medicinal value, among these, *B. alba* Linn. (Cucurbitaceae) has been traditionally used in the treatment of cough, typhoid, pneumonia, inflammation of serous tissues, nervous disorders, rheumatism and jaundice. *B. alba* has also been included in homoeopathic formulations which are in clinical use for its antirheumatic, antiphlogistic and anti-anxiety activities. Despite a long tradition of use of some species, the genus has not been explored properly. In the concluding part, the future scope of *Bryonia* species, has been emphasized with a view to establish their multifarious biological activities and mode of action.

Keywords: Alkaloids, *Bryonia alba*, Flavonoids, Triterpenoids

INTRODUCTION

This review emphasizes the traditional uses and clinical potential of *Bryonia* species. Through this review, authors hope to attract the attention of natural product researchers through out the world to focus on the unexplored potential of the *Bryonia* species. This genus needs to be investigated systematically so that potential species can be exploited as therapeutic agents.

This review has been compiled using references from major databases as Chemical Abstracts, Medicinal and Aromatic Plants Abstracts, Pubmed, King's American Dispensatory, Henriette's Herbal Homepage, Duke's Phytochemical and Ethnobotany.

The available information on *Bryonia* has been divided into six sections, i.e., ethnopharmacology, morphology and microscopy, phytoconstituents, pharmacological reports, clinical studies and toxicology. The ethnopharmacological section has been further subdivided into two sections, i.e., traditional uses, and alternative and complimentary medicinal uses. The reports in which *Bryonia* species have been used as a domestic remedy by common men without any prescription for the treatment of various ailments have been discussed under traditional uses. The subhead "Alternative and Complimentary medicinal uses" highlights *Bryonia* species as medicine prescribed by medical practitioners for the treatment of various ailments. It also mentions uses for which *Bryonia* species or their preparations available in the market. Under every section, *Bryonia* species have been arranged in alphabetical order.

The genus *Bryonia*

Bryonia, the smallest genus in the family Cucurbitaceae, comprises about 12 species distributed throughout the Europe and West Asia (1). The members of *Bryonia* are herbaceous with tuberous roots and flowers in racemes. The species used in medicine are *Bryonia alba* Linn. and *Bryonia dioica* Jacq. Except for *B. alba*, all other species of *Bryonia* are dioecious.

B. alba (White bryony) is found in Central Europe, Deccan and Southern India, and is distinguished from *B. dioica* (Red bryony) by its black fruits and monoecious flowers (2).

Ethnopharmacology

Traditional uses

B. alba has been traditionally used in the treatment of frontal pain, cough, peritonitis, inflammation of serous tissues, typhoid, pneumonia, jaundice, rheumatism, and as heart tonic (3). *B. alba* has also been used in the treatment of facial neuralgia and brain disorders with serous exudation. The fruits of *B. cordifolia* Linn. have been used in diabetes (4).

B. dioica has been used in the treatment of dropsy, bronchitis, tonsillitis, in pleurisy, and as a hydragouge cathartic and diuretic (5). It was formerly used as a purgative, and for the treatment of gout (6). Other indications of the plant are alcoholism, amenorrhea, anger, apoplexy, asthma, brain diseases, affection of inflammed breast, cancer, chill, constipation, cough, dentition, diarrhoea, dyspepsia, eczema, enteric fever, gastroenteritis, haemorrhages, hernia, hiccough, milk fever, whooping cough, nephritis etc. (7).

B. laciniosa Linn. has been used in bilious attacks, and in fevers with flatulence (8). The leaves are applied topically to inflammations. The juice of leaves and roots of *B. palmate* Linn. have been used externally for skin disease in Sri Lanka (9).

B. verrucosa Ait. has high cytotoxicity and been used for antitumour, anti-inflammatory, analgesic and antifertility effects, and also as emetic, purgative and anesthetic agent (10).

Alternative and complementary medicinal uses

B. alba has been included in a number of homoeopathic preparations which are in clinical use. Homoeopathic Materia Medica lists *B. alba* roots for its antirheumatic, antiphlogistic,

expectorant and anti-anxiety activities (11). A homoeopathic medicine containing *B. alba* has been moderately effective orally in curing haematuria affected cows/bullocks, by giving 8-10 drops of medicine for 10 days (12). Homoeopathic complex containing *B. alba* as one of the constituents has been reported to be effective and economical in the management of mastitis in lactating dairy cows (13) and riverine buffaloes (14). *Bryonia* D4 homoeopathic medicine showed encouraging results in the treatment of cases of *E. coli* mastitis in cows (15). It is also used for treatment of chronic obstructive pulmonary diseases such as cough and cancer in smokers (16). Gripp-heel (mixture of *Aconitum*-D4, *Bryonia*-D4, *Lachesis*-D12, *Eupatorium perfoliatum*-D3 and phosphorus-D5) has been reported to be effective in the treatment of common cold (17). 'Loshtak' tablets prepared from standardized powder of *B. alba* roots are used as an adaptogen (18).

Morphology and Microscopy

Bryonia species are climbing herbs, scabrid or glabrous; tendrils 2-fid in the Indian species; leaves petioled, palmately 5-lobed or 3 - 5 angular; flowers small, yellowish, males and females clustered in the same axils (in the Indian species shortly pedicelled); calyx-tube widely companulate, 5-toothed; corolla 5-partite; stamens 3, inserted low down the calyx-tube; anthers three, two 2-celled, one 1-celled, cells curved or somewhat sigmoid; ovary ovoid; style slender, 3-fid at the top, no disc at the base, ovules many, horizontal placenta 3; berry spherical, indehiscent; seeds oblong or ovoid, compressed (19).

B. alba is 6 - 12 feet high; roots thick, tuberculate, yellowish outside, white within; leaves long-petioled; flowers pistillate in long-peduncled racemose corymbs (4, 20). *B. cordifolia* is a perennial twinning shrub with tuberous roots; leaves 3-5 lobed or angled, shining; flowers white; fruits fleshy, ovoid or oblong, bright red when ripe; seeds embedded in red pulp. *B. dioica* spreads from the Mediterranean region into South and Central Europe (2). In India, it is found in Punjab, Uttar Pradesh and Maharashtra (21). The plant is 6 - 12 feet high; roots long, fleshy, branching, white, a finger-thick; leaves ovate or roundish in outline, 5-lobed margin wavy-toothed, rough with callous points, paler beneath; flowers pistillate dioecious, greenish white, corymbose, short-peduncled (1); fruits small, red, poisonous berries (22). *B. laciniosa* is a slender, nearly glabrous climber, annual, rough or smooth; stems angular, slender tendrils; leaves 4 - 6 inches, deeply 5-lobed, often rough and dotted above; stalk as long as the blade; flowers small, yellowish, male and female flowers clustered together; fruit three-fourth inch in diameter, sessile; seeds ovoid (19, 23). *B. palmata* is climbing, grooved, glabrous; leaves upto 8 × 5.5 cm, membranous, deeply 5-lobed; male flowers many, yellow, female flowers solitary or few; fruits globose, yellowish green; seeds grey, thick (9). *B. scabrella* Linn. is a climbing annual; leaves 3 to 5-lobed; flowers yellow, male flowers in clusters; fruits globose, small, bright red when ripe (20). *B. umbellata* Klein. is an extensively spreading climber with glabrous, much branched stems; leaves rigid, highly variable in size and shape, upper surface green, lower surface glaucous-white; flowers pale yellow; fruits oblong, slightly angular, green to yellow (4, 24). The transverse section of *B. dioica* root exhibits a fine line separating a narrow bark from a large, fleshy wood; the latter contains, more or less uniformly distributed small groups of vessels, radially arranged and extending from the centre to the bark (25). The powdered drug is pale yellowish-orange to pale yellow; comprises fragments of parenchyma, numerous starch grains, both simple and 2-6 compound, individual grains spheroidal, plano-convex and polygonal usually with a central hilum, and from 4 to 25 μ in diameter, frequently with a central cleft; fragments of broad tracheae up to 250 μ in width, reticulate or with bordered pore markings; large yellow cork fragments (5).

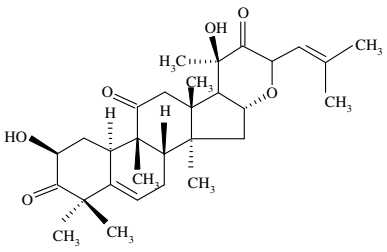
Phytoconstituents

Six species of *Bryonia* have been investigated phytochemically. Table 1 summarizes the phytoconstituents of various species of *Bryonia*.

Table 1: *Phytoconstituents of various species of Bryonia.*

Species	Phytoconstituents
B. alba Linn.	**Alkaloid** bryonicine (26); **flavonoids** (27-29) saponarin, vitexin, isovitexin, 5, 7, 4'-trihydroxy flavone 8-C-glucopyranoside, lutonarin, isoorientin; **glycosides** (30) 22-deoxocucurbitosides A **[1]** and B, 22-deoxocucurbitacin D **[2]**; **triterpenoids** (30, 31) cucurbitacin L **[3]**, 23, 24-dihydrocucurbitacin B, 23, 24-dihydrocucurbitacin D **[4]**, arvenin IV; **lipids** (32-34); **proteins** (35)
B. cretica Linn.	**Triterpenoids** cucurbitacins E **[5]**, I **[6]** and L **[3]**; **sterol glycoside** β-sitosterol-3-O-glucoside (36, 37)
B. dioica Jacq.	**Essential oil** (38); **glycosides** (39-49) bryonoside **[7]**, bryoside **[8]**, cucurbitacin S **[9]**, cucurbitacin L **[3]**, cucurbitacin J **[10]**, cucurbitacin K **[11]**, tetrahydrocucurbitacin I **[12]**, bryoniosides A-G **[13-19]**, cabenoside D **[20]**, bryoamaride **[21],** bryodulcoside **[22]**, alliaroside, bryogenin **[23]**; **triterpenes** (50, 51) bryocoumaric acid **[24]**, 3α-hydroxy-multiflora-7, 9 (11)-dien-29α-oic acid **[25]**; **triterpene alcohols** (52-56) tirucalla-5, 24-dien-3β-ol, 24-methyltirucalla-5, 24 (24')-dien-3β-ol; **saponins** (57) brydiosides A **[26]**, B and C; **flavonoids** (58) saponarin, vicenin 2; **fatty acids** (59, 60) methyljasmonate, α-linolenic acid; **protein** lectin (61, 62); bryodiofin (63), Bryodin (64); Δ^7-stigmastenol (65); **Asparagine derivative** N^4-(2-hydroxyethyl)-L-asparagine (66)
B. melanocarpa Nab.	**Triterpenoids** (67-69) cucurbitacin L **[3]**, bryoamaride **[21]**, isomultiflorenol, bryonolic acid; **phytosterols** (24R)-24-ethyl-5α-cholest-7-en-3β-ol, stigmasta-7E, 24 (28)-dien-3β-ol, 4α-methyl stigmasta-7E, 24 (28)-dien-3β-ol; **sterol glycosides** (68) (24R)-24-ethyl-5α-cholest-7-en-3β-ol 3-O-β-D-glucopyranoside

B. multiflora Boiss & Heldr.	**Triterpenoids** cucurbitacin B **[27]** and I **[6]** (70); **fatty acids** (71)
B. verrucosa Ait.	**Tetracyclic triterpenoid** cucurbitacins (10)



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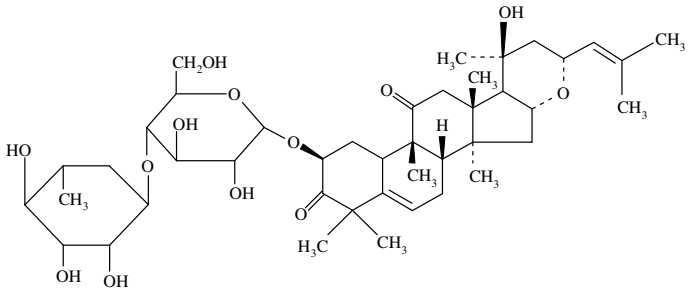

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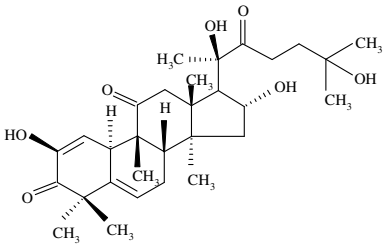

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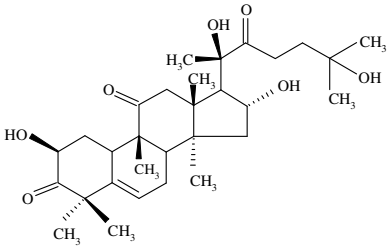

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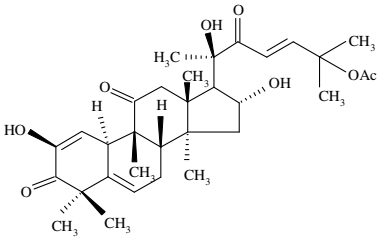

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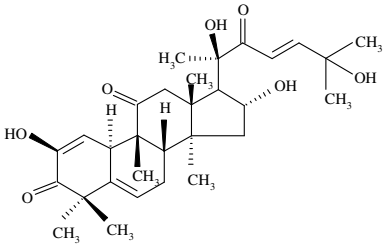

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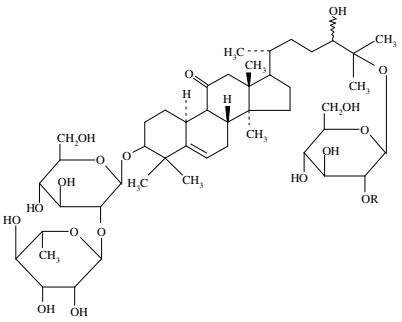
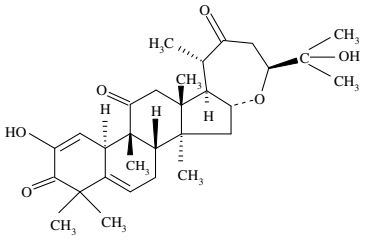


7 **R = glucosyl**
8 **R = H**



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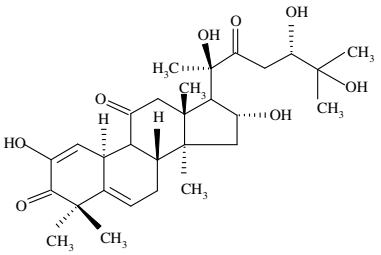

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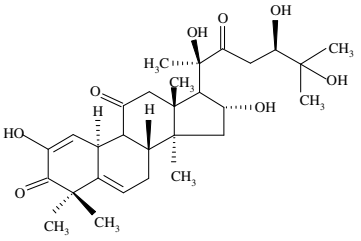

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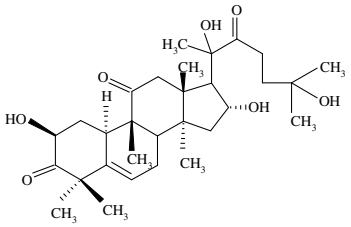

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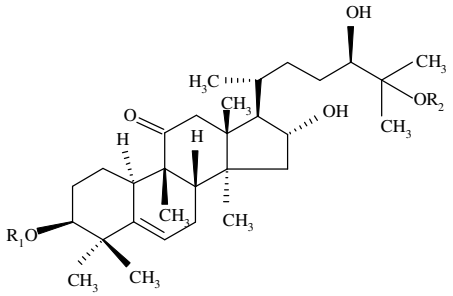
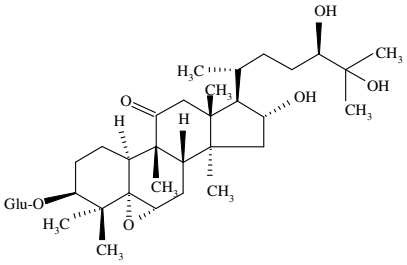


	R_1	R_2
13	H	Glu
14	α-L-rhamnopyranosyl(1-2)Glu	H
15	α-L-rhamnopyranosyl(4-Ac)(1-2)Glu	H



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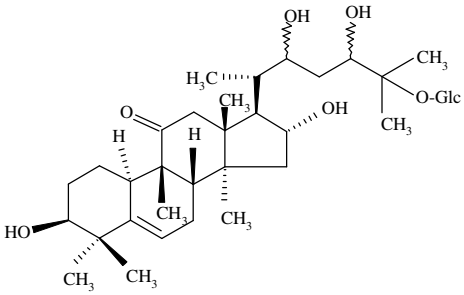

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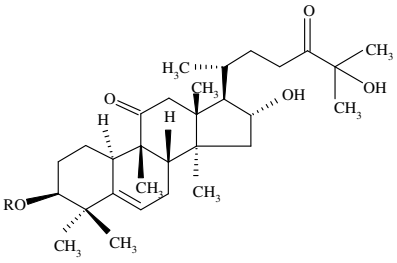
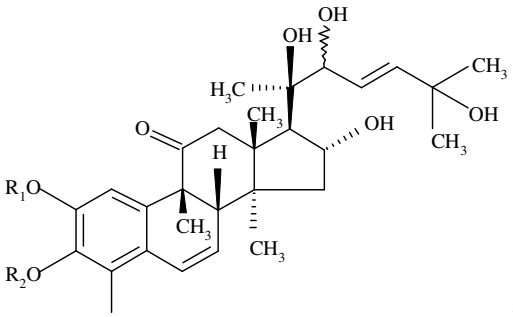
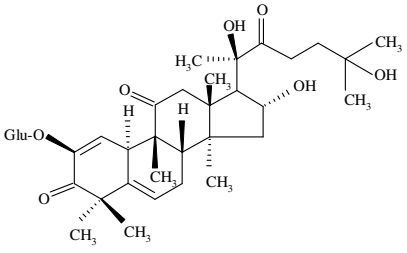


	R
18	Glu
19	α-L-rhamnopyranosyl(1-2)Glu



	R_1	R_2
20	Glu(1-2)Glu	Glu



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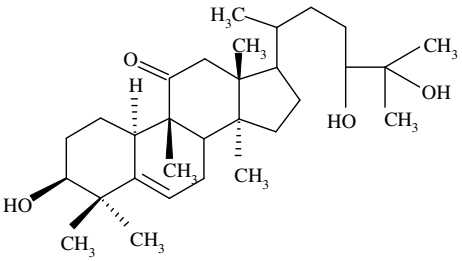

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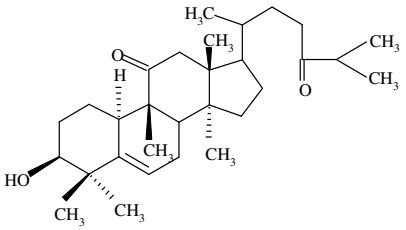

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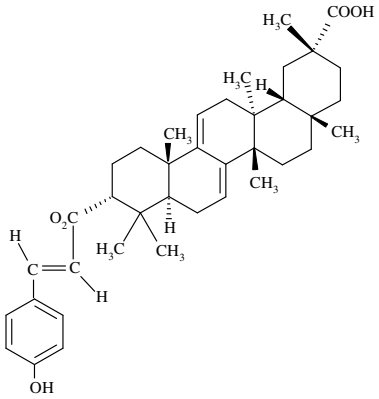

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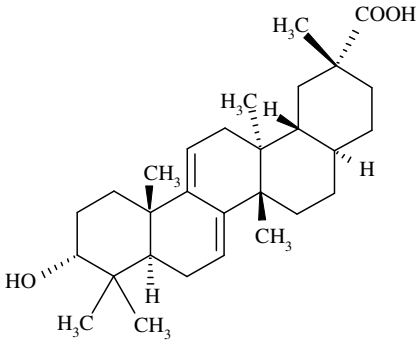

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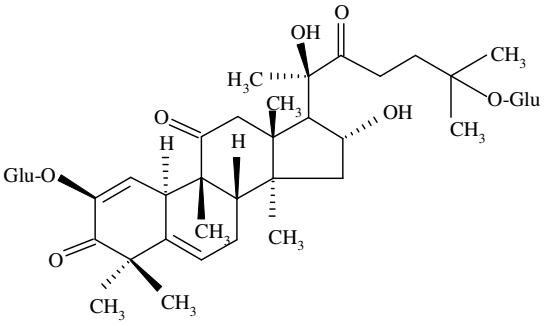

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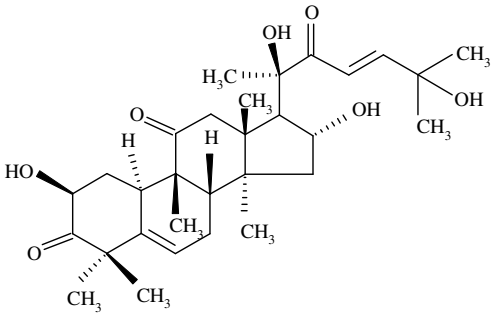

27

Structures of various phytoconstituents of Bryonia species

Pharmacological reports

The available literature reveals that amongst 12 species of *Bryonia*, only three species, i.e., *B. alba*, *B. dioica* and *B. syriaca* have been evaluated for their pharmacological activities. Eight major components of a fraction of unsaturated polyhydroxy fatty acids, isolated from *B. alba* roots, have been reported to exhibit prostaglandin-like activity on isolated strips of rat colon at the dose of 1.1×10^{-5} g with reference to $PGF_{2\alpha}$ (10^{-8}g) (34). Cucurbitacins and trihydroxydecadienoic acids from *B. alba* roots exhibited multiple effects on eicosanoid system thereby justifying its use in the treatment of many diseases (72). 23, 24-dihydrocucurbitacin D (DHCD) isolated from *B. alba* has been reported to inhibit NO generation by blocking nuclear factor kappa B activation and inducible NO synthase transcription in mouse peritoneal macrophages at < 80 μM (73). This study gave a clue that DHCD and its derivatives could be developed as anti-inflammatory drugs. *B. alba* roots exhibited antidiabetic effects by normalizing blood phospholipids and lipid peroxidation in liver of rats with alloxan diabetes (74, 75). It has been reported that methanol extract of *B. alba* (5 mg/kg) and the butanol fraction containing trihydroxyoctadecadienoic acids (0.05 mg/kg) decreased blood sugar in alloxan diabetic rats after 20 days of daily intramuscular treatment (33, 76, 77). Effects of trihydroxyoctadecadienoic acids on the activity of glycogen phosphorylase (a- and b-forms), phosphoprotein phosphatase and hexokinase in liver and muscle tissues of white rats with alloxan diabetes were considered possible mode of action (76). A standardized mixture of isomeric trihydroxy fatty acids, isolated from *B. alba* roots, exhibited antiatherosclerotic effects in the cell culture obtained from

atherosclerotic plaques of the human aorta (78). Cucurbitane glycoside (Askenoside B) isolated from *B. alba* exhibited highly potent tyrosine inhibition activity, thus, inferring its importance in cosmetic industries as skin whitening agent (79). Cucurbitacins isolated from *B. alba* have been reported to exhibit cytotoxic and antitumour activity (80-82). It has been reported that *B. alba* do not increase salivary NO and cortisol in atheletes even after heavy physical exercise (83). These results confirm stress protection effect of *B. alba*. Canova (homoeopathic dilutions of *Aconitum nagellus*, *Arsenicum album*, *B. alba*, Lachensis muta venom and *Thuja occidentalis*) has been reported to stimulate immune system by activating macrophages (84-86). Activated macrophages stimulate the lymphocytes, thereby increase their cytotoxic action. Further, Seligmann et al. (84) reported that Canova method is devoid of cytotoxicity or genotoxicity at the chromosomal level as it did not affect mitotic indexes and chromosomal aberrations. Aqueous and methanol extracts of *B. alba* roots did not show any evidence of genotoxic effect (87).

A widely used Egyptian folk herbal preparation containing *B. cretica* as one of the constituents exhibited hypoglycaemic activity in male alloxanized rats (88). Bryodin, a single chain ribosome-inactivating protein isolated from *B. cretica* was found to selectively inhibit the growth of persistently HIV-1-infected T lymphoma cells and human lung fibroblast in the concentration of 2-20 µg/ml (89). The cucurbitane glycosides bryoniosides A-G, cabenoside D and bryoamaride, isolated from the roots of *B. dioica*, exhibited anti-inflammatory activity (41). Only hydroxylated analogue of bryonioside A exhibited inhibitory effects on Epistein-Barr virus early antigens, thus, confirming its antiviral activity. A toxic protein bryodin, isolated from *B. dioica*, has been used in the construction of immunoconjugates directed against the human tumor cells (63). Two ribosome inactivating proteins Bryodin I and Bryodin II, isolated from *B. dioica,* constructed as immunoconjugates with the chimeric form of BR96, a carcinoma reactive internalizing antibody (90). These were found to bind and kill BR96 antigen positive carcinoma cells. Bryodin L, isolated from the leaves of *B. dioica*, exhibited cytotoxic activity by inhibiting protein synthesis by a rabbit reticulocyte lysate and phenylalanine polymerization by isolated ribosomes and altering rRNA in a similar manner as the A chain of ricin and related toxins (91). It also exhibited cytotoxic action to the Thy 1.1-expressing mouse lymphoma cell line AKR-A *in vitro* (92). Ethanolic extract of *B. dioica* exhibited antiherpic effect on multiplication of human herpesvirus and poliovirus-2 in cell cultures (93).

The methanol extract of *B. laciniosa* exhibited significant analgesic activity in rats using hot plate and acetic acid-induced writhing methods (94). The extract also exhibited antipyretic activity evaluated by normal body temperature and yeast-induced hyperpyrexia in rats. The chloroform extract of *B. laciniosa* (200 mg/kg) exhibited significant anti-inflammatory activity in carrageenan-, dextran-, histamine- and serotonin-induced hind paw oedema in rats, and cotton pellet induced granuloma (95).

The butanol extract (4 mg/disc) of *B. syriaca* showed moderate antifungal activity against *Aspergillus flavus, Fusarium moniliforme* and *Candida albicans* relative to miconazole nitrate at 40 µg/disc (96).

Clinical Studies

In clinical trials, hydroalcoholic extract of *B. alba* roots showed adaptogenic, immunomodulatory, stress-protective, and tonic properties by increasing the non-specific resistance (97, 98). *B. alba* mother tincture (a homoeopathic medicine) enhanced significantly the activity of phagocytosis of human granulocytes *in vitro* tests and controlled single-blind studies (99). A monocentre randomized placebo-controlled study showed that complex of homoeopathy (containing *B. alba*) was not superior to placebo in reducing 24h morphine consumption after knee ligament reconstruction (100). A plant-based formulation containing *B. alba* was found to be effective in the management of chronic obstructive pulmonary disease in a randomized double-blind placebo-controlled study (101). A double-blind placebo-controlled study was performed to assess the effectiveness of homoeopathic *Bryonia* 9CH in the treatment of pain due to unwanted lactation (102). A significant improvement of lactation pain, breast tension and spontaneous milk flow was observed after therapy.

Toxicology

The aqueous extract of *B. alba* roots produced impairment of the action of frog's heart (103). In mammals (cats and dogs), aqueous extract produced a fall of blood pressure. The fresh roots of *B. alba* are extremely irritating, causing blisters when bruised and kept in contact with skin, and cause serious gastro-intestinal inflammation when taken internally (3). Profuse and uncontrollable diarrhoea, vomitting, vertigo, reduction of temperature, dilatation of the pupils, cold perspiration extremely feeble pulse, colic, collapse, and death have resulted from its use. *B. cretica* has been found to possess a depressant action on the heart as well as on the plain muscle (103). The resin derived from the plant caused gastro-intestinal irritation. The minimum lethal dose of the dry extract of *B. cretica* is 100 mg per kg, subcutaneously, for rabbits, and 75 mg per kg, intravenously, for dogs. The resinous material of *B. dioica* roots as well as the products obtained by its successive extraction with light petroleum ether, chloroform and ethyl acetate produced marked purgation in doses of 1 g (103). The fruit extract of *B. dioica*, obtained in phosphate buffer saline, in mild conditions, showed a strongly toxic activity after i.p. injection of 0.4 mgper Balb/c mice that was killed in 18 min (63). The lethal effect was attributed to a protein, brydiofin.

CONCLUSION

About 12 species of the genus *Bryonia* have been reported in various floras. An exhaustive survey of literature revealed that sporadic information is available on 10 species. Among these 10 species, most of ethnopharmacological reports are available on *B. alba and B. dioica*. Further, only 6 species of *Bryonia* (Table 1) have been partially investigated for their phytoconstituents.

A close scrutiny of literature on *Bryonia* reveals that 5 species have been investigated pharmacologically. Pharmacological

studies infer that *B. alba* exhibits anti-inflammatory, antiatherosclerotic and cytotoxic properties; *B. cretica* exhibits antidiabetic property; *B. dioica* possesses anti-inflammatory, antiviral and antitumour activities; *B. laciniosa* possesses analgesic, antipyretic and anti-inflammatory activities; and *B. syriaca* displays antifungal activity.

B. alba has been included in number of herbal and homoeopathic formulations, which are in clinical use for the treatment of various ailments. Mother tinctures of the plant are available in Indian market, and is frequently used for the treatment of CNS disorders, but no pharmacological work supports its efficacy in CNS disorders. Keeping in view the traditional, alternative and complimentary medicinal uses, sporadic phytochemical and pharmacological reports, low toxicity, and frequency of use in homoeopathic formulations, *B. alba* seems to hold great potential for in depth investigation for various biological activities, especially its effect on the central nervous systems.

Few preliminary pharmacological reports support medicinal potential of some *Bryonia* species. These species need to be investigated systematically with a view to establish their varied pharmacological activities and mode of actions.

ACKNOWLEDGEMENT

The authors acknowledge the financial assistance provided by University Grants Commission, New Delhi to Suresh Kumar for the compilation of this review.

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