https://doi.org/10.31925/farmacia.2024.1.2 REVIEW

BRYONIA ALBA L. - A PROSPECTIVE MEDICINAL PLANT OF THE *CUCURBITACEAE* FAMILY

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Abstract

The *Cucurbitaceae* family, encompassing a diverse array of plants, holds immense significance across the agricultural, food, and pharmaceutical sectors. Within this botanical family, *Bryonia alba* L. stands out as a prominent representative, contributing substantially to various industries on a global scale. *Bryonia alba's* widespread distribution has established it as a reliable raw material base, garnering attention from researchers and scientists in numerous countries. This review article summarises the major scientific literature from 1968 to 2022, particularly the period from 2000 to 2022. Several research databases, including Scopus, Google Scholar, and PubMed, provided summaries of the data that were collected for this review. This review summarises the literature on the botanical characteristics, chemical composition, medicinal uses, and pharmacological actions of *Bryonia alba*. It thoroughly examines the species' phytochemical constituents, traditional and homoeopathic applications, and the diverse biological activities attributed to its compounds, particularly cucurbitacins. The review also highlights the need for further research to fully understand the therapeutic potential and safety profile of *B. alba*, acknowledging its significant role in various medicinal systems.

Rezumat

Familia *Cucurbitaceae* prezintă o importanță deosebită pentru sectoarele agricole, alimentare și farmaceutice. În cadrul acestei familii botanice, *Bryonia alba* L. este un reprezentant important, cu o răspândire largă. Acest articol de analiză literatura științifică din perioada 1968-2022, utilizând mai multe baze de date de cercetare, inclusiv Scopus, Google Scholar și PubMed. Acest studiu analizează literatura de specialitate privind caracteristicile botanice, compoziția chimică, utilizările medicinale și acțiunile farmacologice ale speciei *Bryonia alba*, examinând în detaliu constituenții fitochimici, aplicațiile tradiționale și homeopate și diversele activități biologice atribuite compușilor săi, în special cucurbitacinele. De asemenea, analiza evidențiază necesitatea unor cercetări suplimentare pentru a înțelege pe deplin potențialul terapeutic și profilul de siguranță al *B. alba*.

Keywords: *Bryonia alba* L., pharmacological activity, biologically active compounds, cucurbitacins

Introduction

Medicinal plants, with their profound historical roots, continue to be integral components of both traditional healing practices and modern medicine. The enduring importance of these botanical resources lies in their diverse array of bioactive compounds. This introduction delves into the critical role of medicinal plants, highlighting their significance in contemporary medicine and their enduring value in traditional healing, drawing insights from authoritative sources in the field.

The World Health Organisation (WHO) recognises the pivotal role of medicinal plants in global healthcare, emphasizing their contribution to prevention and disease management [1]. Traditional medicine, often centred around the use of medicinal plants, remains a primary healthcare resource for a substantial portion of the world's population, particularly in regions where access to modern medical facilities may be limited [2].

Scientific research has increasingly validated the efficacy of medicinal plants, shedding light on their potential in treating a wide spectrum of ailments. The integration of traditional knowledge with modern scientific methodologies has led to the discovery of novel compounds and the development of pharmaceuticals rooted in plant sources [3].

In modern medicine, medicinal plants are not merely relics of the past; they are actively explored for their potential in drug discovery and development. The recognition of their therapeutic properties has led to the isolation, identification, and synthesis of active compounds, contributing to the development of drugs with applications ranging from pain management to cancer treatment [4].

As we navigate the intricate relationship between medicinal plants and human health, it becomes evident that their importance transcends cultural traditions. From providing essential remedies in traditional settings to serving as a wellspring of innovative pharmaceuticals in modern laboratories, medicinal plants continue to shape the landscape of healthcare worldwide.

Bryonia alba L. belongs to the family *Cucurbitaceae*, subfamily *Cucurbitoideae*, tribe *Bryonieae*, and genus *Bryonia*. Recent molecular phylogenetic studies [5] of the *Cucurbitaceae* family show that the genus *Bryonia* includes 10 species: *B. acuta, B. alba, B. aspera B. cretica, B. dioica, B. marmorata, B. monoica, B. multiflora, B. syriaca,* and *B. verrucosa* [5, 6].

Studies on major chloroplast haplotypes of the *Bryonia* genus indicate that this genus is the *Cucurbitaceae* clade centred in the Mediterranean, the Irano-Turanian, and (in part) the Holarctic floral kingdoms [5-7]. All *Bryonia* species are well adapted to drained soils, such as dunes, dry channels, or rocky slopes in mountainous areas, thanks to the presence of underground tubers for water storage [6, 7].

B. alba L. is one of the more common species of the genus. Its life-form is liana, and it is a perennial herbaceous monoecious plant. *B. alba* applies to both wild plants and cultivars [4-6, 8].

This review aims to present a thorough and up-to-date survey of literature on the widespread species *B. alba*, based on peer-reviewed research publications, with emphasis on phytochemistry, biological activity, traditional medicinal use, probable toxicity, and side effects. Such an overview can help scientists everywhere learn more about *B. alba* and open new avenues to study the poorly understood phytochemical components and biological functions of this species. This overview covers the period from 1968 to 2022, particularly the period from 2000 to 2022, and it includes all reported literature. Several research databases, including Scopus, Google Scholar, and PubMed, provided summaries of the data that were collected for this review.

Botanical characteristics.

B. alba stems are numerous, 2.0 - 4.0 m long. They are rigidly pubescent, furrowed, and creeping, clinging using unbranched spiral tendrils. The leaves are alternate, with long petioles, ovate, five-lobed; they are toothed on the edge, with a heart-shaped base, with a rough surface, up to 10.0 cm long. Flowers are separate, regular, in axillary inflorescences, yellowish-white. Female flowers are collected in corymb-like or umbrella-like inflorescences. The male flowers are collected in whisks located at the tops of the stems. Fruits are black, spherical, juicy berries, 8.0-10.0 mm in diameter, with 10 ovate flattened seeds. Unripe fruits are green. *B. alba* has a rod-root system. Roots are thick and fleshy. The root length can reach 50.0-70.0 cm with a width of up to 10.0 cm. The surface of the root is transversely wrinkled and has intermittently ringed grooves. The colour of the root surface is yellowish-grey. The cut colour is white with milky juice [4, 8, 9].

The medicinal plant material (MPM) of *B. alba* is the root (*Bryoniae radix).* Harvesting is carried out before vegetation or at the end of vegetation, as 2-3-year-old plants are preferred. Soil is removed from the roots, which are used fresh or finely sliced and dried [6, 8]. MPM must be kept separately from others, by the rules for the storage of poisonous plants.

Chemical composition

The most studied part of *B. alba* is the roots. *B. alba* roots contain cucurbitacins, tetracyclic triterpenes found in plants in the form of aglycones and glycosides [10-13]. The sugar part of the glycosides is most commonly glucose and rhamnose. Glycosides of cucurbitacins are known to be unstable and will split into aglycones when raw materials are dried [14, 15].

Cucurbitacin E, B, D, I, J, K, L, R, dihydrocucurbitacin B, D, E, tetrahydrocucurbitacin I, 22-deoxocucurbitacin D, rhamnoglucosyl-22-deoxo-16,23-epoxycucurbitosides (A and B), 23, 24-dihydrocucurbitacin B, 23, 24- dihydrocucurbitacin D and arvenin IV have all been found in *B. alba* roots [14, 16-24].

HPLC and spectrophotometric methods are used to determine the quantitative content of cucurbitacins in MPM and extracts from *B. alba* roots [25].

The other triterpene of the *B. alba* roots, besides tetracyclic triterpenes, is bryonolic acid (pentacyclic triterpene) [23, 26, 27].

Information about the compounds responsible for the poisonous activity of *B. alba* is controversial. Many articles say that the cucurbitacins are the most poisonous substances in *B. alba* [6, 19, 21, 28]. Other sources identify not only cucurbitacins but a complex of toxic compounds, including the glycosides bryonin, bryonidin, and bryonicin, which are found in all parts of *B. alba*, especially in the roots and fruits [29]. Manvi *et al*. [30] proved the presence of alkaloids, saponins, steroids, triterpenoids, carbohydrates, and proteins in various extracts of *B. alba*.

Panosyan *et al*. [31] confirmed the presence of phytosterols and their glycosides in the roots of *B. alba*, namely cholest-7-en-3-ol, 24-methylcholest-7-en-3-ol, 24-ethylcholest-7-en-3-ol, 24-methylene-cholest-7-en-3-ol, 24-ethylidenecholest-7-en-3-ol, 24-ethyl-4-methylcholest-7-en-3-ol, 24-ethylidene-4-methylcholest-7-en-3-ol, and 3-O-glucopyranosides. The lipid composition of the roots of *B. alba* was studied: it consists of fractions of 3-acyloxy-24-alkyl(alkenyl)-cholest-7-enes, triacylglycerols, 1,2-diacyl-3-monoglycopyranosyl- sn-glycerol, 1,2-diacyl-3-diglycopyranosyl-sn-glycerol, 1,3-bis(3-sn-phosphatidyl)glycerol, 3-sn-phosphatidylethanolamine, 3-sn-phosphatidylcholines and methyl esters of fatty acids [32]. The content of unsaturated fatty acids in the fraction was 60.94%, with the main component being linolenic acid [33].

Vartanian *et al*. [32] and Panossian *et al.* [33] confirmed the presence of fatty acids (especially trihydroxyoctadecadienoic acids) in *B. alba* roots. Panossian *et al*. [32, 33] identified eight major components of the unsaturated polyhydroxy fatty acid fraction isolated from *B. alba* roots as four diastereoisomeric pairs of 9,12,13-trihydroxy-10E,15Z-octadecadienoic; 12,15,16-trihydroxy-9Z,13E-octadecadienoic; 9,10,13-trihydroxy-11E,15Z-octadeca-dienoic and 12,13,16-trihydroxy-9Z,14E-octadeca-dienoic acids.

Orekhov *et al*. [34] isolated a mixture of isomeric trihydroxy fatty acids from *B. alba* L. roots, including 12,13,16-trihydroxy-9Z,14E-octadecadienoic acid, 12,15,16-trihydroxy-9Z,13E-octadecadienoic acid, 9,10,13-trihydroxy-HE, 15Z-octadecadienoic acid, and 12,13,16-trihydroxy-9,14Z-octadecadienoic acid. Karageuzyan *et al*. [35] reported about isomers of 12,13,16-trihydroxy-9Z,14E-octadecadienoic acid, 12,15,16-trihydroxy-9Z,13E-octadecadienoic acid, 9,10,13-trihydroxy-11E,15Z-octadecadienoic acid, and 9,12,13-trihydroxy-10E,14Z-octadecadienoic acid. We found some differences in the fatty acids' names in all mentioned reports. We note the prospects of recent studies of trihydroxyoctadecadienoic acids and can propose, for now, to name fatty acids from *B. alba* roots like trihydroxyoctadecadienoic acids, without specification. Lectins have also been found in the roots of *B. alba* [36].

Our literature search revealed that the root of *B. alba* contains oxidised tetracyclic triterpenes, polyunsaturated hydrocarbons, phospholipids, phosphatidylcholines, essential oils, fatty acids, amino acids, enzymes, sugars, carotene, and vitamins C and E [37].

Recent studies show that sugars are present in *B. alba* roots in free and bound forms. Sucrose, fructose, galactose, and glucose have been found before hydrolysis. Fructose is the most prominent of these - 25.03 mg/kg. Rhamnose, arabinose, fucose, glucose, and galactose have been found after hydrolysis, where the content of glucose (152.55 mg/kg) prevails [38].

The qualitative composition and the quantitative content of free and bound amino acids from *B. alba* roots were determined using HPLC. One study shows that at least 14 compounds contain free amino acids; the bound amino acids have at least 16 links. The arginine content (8.30 µg/mg) in the free amino acids exceeded that of the others. Glutamic acid (11.42 µg/mg), asparagine (9.38 µg/mg) and cysteine (8.43 µg/mg) were detected in the highest amounts in the bound acids [39].

Macro and micro elements in *B. alba* roots have also been studied, as they are determined by the atomic absorption spectrometry method. Studies show the presence of at least 19 elements and the absence of heavy metals in *B. alba* roots. The most common element among the elements studied was K, followed by Ca, Mg, P, Si, Fe, Na, and Zn. Hg, As, Cd, Co, Mo, and Pb were only detected in trace amounts [41, 42].

The aerial parts of *B. alba* are less studied. The report of Ielciu *et al.* [42] concludes that the aerial parts of *B. alba* do not contain cucurbitacins, but that there are significant levels of flavonoids and phenols. Different studies of flavonoids in the aerial parts of *B. alba* showed the presence of four main flavonoids: lutonarin, saponarin, isoorientin, isovitexin, and 5, 7, 4'-trihydroxy flavone 8-C-glucopyranoside [42-45]. Furthermore, Ielciu *et al.* [46] found the presence of four flavonoids (lutonarine, saponarine, isoorientine, and isovitexine), and their structures were elucidated by MS and NMR in leaves of *B. alba*. The most significant elements in *B. alba's* chemical components are listed in Table I.

Medicinal uses of *B. alba*

It's widely known that *Bryonia* preparations are commonly used in homoeopathic medicine. The tincture of *B. alba* roots is included in many homoeopathic pharmacopoeias of the world: India, Britain, the USA, Germany, and France. There is some variance in the technologies used to obtain the tincture. The Pharmacopoeia of India, for example, requires the use of dry roots of *B. alba,* whereas other pharmacopoeias use fresh roots for the tincture preparation [47-50]. *B. alba* is also used in homoeopathy in the form of granules, drops, ointments, oils, and opodeldoc [9, 22, 51, 52]. Homoeopathy medicines from *B. alba* roots are used as anti-inflammatory, antipyretic, antibacterial, and muscle relaxant preparations, as well as to treat bronchitis, pneumonia, measles, and rheumatism [6, 9, 51-54]. These effects are primarily related to cucurbitacin and bryonin content [6, 46, 52, 53].

B. alba root tincture, infusion, decoction, fresh juice, and root powder are used in folk medicine in Europe and Asia as a painkiller, diuretic, laxative, haemostatic, and local irritant; also, in small doses, it is used as a CNS suppressor [6, 52, 54].

Table I

The most significant active ingredients present in the *B. alba* composition

Part use	Chemical class	Active ingredients	References
Roots	Tetracyclic triterpenes	Cucurbitacin E, B, D, I, J, K, L, R, dihydrocucurbitacin B, D, E, tetrahydrocucurbitacin I, 22-Deoxocucurbitacin D, rhamnoglucosyl-22-deoxo-16,23-epoxycucurbitosides (A and B), 23, 24-dihydrocucurbitacin B, 23, 24- dihydrocucurbitacin D, arvenin IV	[14, 16-24]
Roots	Pentacyclic triterpene	Bryonolic acid	[23. 26, 27]
Roots and fruits	Glycosides	bryonin, bryonidin, and bryonicin	[29]
Roots (various extracts)	Alkaloids, Saponins, Steroids, Triterpenoids, Carbohydrates, Proteins	Alkaloids, Saponins, Steroids, Triterpenoids, Carbohydrates, Proteins	[30]
Roots	Phytosterols and their glycosides	Cholest-7-en-3-ol, 24-Methylcholest-7-en-3-ol, 24-Ethylcholest-7-en-3-ol, 24-Methylenecholest-7-en-3-ol, 24-Ethylidenecholest-7-en-3-ol, 24-Ethyl-4-methylcholest-7-en-3-ol, 24-ethylidene-4-methylcholest-7- en -3-ol, 3-O-Glucopyranosides	[31]
Roots	Lipids	3-Acyloxy-24-alkyl(alkenyl)-cholest-7-enes, Triacylglycerols, 1,2-Diacyl-3-monoglycopyranosyl- sn-glycerol, 1,2-Diacyl-3-diglycopyranosyl-sn-glycerol, 1,3-Bis(3-sn-phosphatidyl)glycerol, 3-Sn-phosphatidylethanolamine, 3-Sn-phosphatidylcholines	[32]
Roots	Fatty acids	Trihydroxyoctadecadienoic acids Linolenic acid	[25, 32-35]
Roots	Carbohydrate-binding proteins	Lectins	[37]
Roots	Free sugars	Sucrose, fructose, galactose, and glucose	[39]
	Bound sugars	Rhamnose, arabinose, fucose, glucose, and galactose	
Roots	Free amino acids	asparagine, glutamic acid, serine, histidine, glycine, arginine, alanine, tyrosine, valine, phenylalanine, isoleucine, leucine, lysine, proline	[40].
	Bound amino acids	asparagine, glutamic acid, serine, histidine, glycine, threonine, arginine, alanine, tyrosine, cysteine, valine, phenylalanine, isoleucine, leucine, lysine, proline	
Roots	Macro- and microelements	Fe, Si, P, Al, Mn, Mg, Pb, Ni, Mo, Ca, Cu, Zn, Na, K	[41, 42]
Aerial parts and leaves	Flavonoids	Lutonarin, saponarin, isoorientin, isovitexin, 5, 7, 4'-trihydroxy flavone 8-C-glucopyranoside	[43-47]

B. alba roots are used in traditional Turkish, Bulgarian, and Italian medicine to cure rheumatic pains and are also applied to aching joints for their anti-inflammatory properties [55, 56]. In the past, alcoholic extracts of roots, called "*Tinctura Bryoniae*" or "*Bryoniae radix*", were administered to patients with dropsy, and in higher doses to relieve pain and cough brought on by pleurisy [7].

Additionally, in another study, homoeopaths were used in various formulations in the clinic for anti-rheumatic, anti-inflammatory, and anxiolytic activities [22]. These effects are described by the content of the alkaloid bryonicin; flavonoids saponarin, vitexin, isovitexin, 5, 7, 4'-trihydroxyflavone 8-cglucopyranoside, lutonarin, isoorientin; glycosides 22-desoxocucurbitoside A and B, 22-desoxocucurbitacin D; triterpenoids cucurbitacin L, 23, 24-dihydrocucurbitacin B, 23, 24-dihydrocucurbitacin D, arvenin IV; lipids; proteins [20, 21, 36, 43-45]. The various herbal preparations of *B. alba* used to treat bronchitis, COPD, and other respiratory diseases, and a process for their manufacture have been described in a US patent [57].

B. alba roots have been used to heal a variety of ailments including gastroenterological disorders, stomach ulcers, headaches, migraines, depression, forgetfulness, absent-mindedness, and neuro-psychological disorders such as psychosis and hysteria. The oxygen consumption of the heart, liver, and mitochondrial fraction in young and old rats is also significantly increased by *B. alba*, similar to Korean ginseng. Under immobility stress, *B. alba* reduces lipid peroxidation [57].

B. alba roots are used in medicine in different countries. For example, *B. alba* is included in the

Australian list of medicinal drugs that are allowed for use as an active or auxiliary component [58].

Panossian *et al*. [23] reported that *B. alba* roots have adaptogenic properties. Bryonia extract (tablets prepared from a standardised powder of *B. alba* root), called "Loshtak", where the main components are cucurbitacins, has immunomodulatory, stress-protective, and tonic properties that increase the nonspecific resistance of an organism toward harmful stimuli. Clinical trials show that the Bryonia extract was effective in treating workers at the Chornobyl Nuclear reactor who suffered from vegetative-vascular dystonia and other accompanying illnesses that resulted from that facility's well-known accident. It was also effective in preventing radiation-induced disorders and cytostatic side effects in cancer therapy. The use of Bryonia extract in healthy athletes increases their endurance, working capacity, and heart rate restoration after a high physical workload. No side effects caused by Bryonia extract intake were recorded during these trials. Also, some medicines derived from *B. alba* roots such as Gripp-Heel (a combination of Aconitum-D4, Bryonia-D4, Lachesis-D12, Eupatorium perfoliatum-D3 and Phosphorus-D5) are effective in treating the common cold [59].

A recent systematic review examined the use of the juice of *B. alba* berries to treat constipation and oedema. As suggested in the same review, *B. alba* root has also been suggested to treat gout, epilepsy, paralysis, dizziness, hysteria, wounds, burns, tetanus, pain, ulcers, parasitic worms, and cough [60].

Cucurbitacin's pharmacological action

The majority of cucurbitacins have potent biological effects that vary depending on the target cell, including cytotoxic, antitumor, hepatoprotective, anti-inflammatory, antibacterial, anthelmintic, cardiovascular, and antidiabetic effects. Both *in vivo* and *in vitro* studies of the most commonly used cucurbitacins have examined these activities [10-13, 61-65]. For example, cucurbitacin glucosides B/E have been shown to have antioxidant properties and the ability to scavenge free radicals [11, 65]. In addition, several cucurbitacins have analgesic or anti-inflammatory properties [11, 66-69]. Furthermore, several studies have demonstrated a synergistic interaction between cucurbitacins and well-known chemotherapy drugs such as doxorubicin and gemcitabine [10, 70, 71].

Recent research has shown that cucurbitacin can inhibit the JAK/STAT-3 signalling pathway, thus preventing T lymphocyte recruitment and the hyperinflammatory state in COVID-19 [72, 74].

Pharmacological action of B. alba (analysis of reports)

B. alba and its bioactive components have numerous benefits and could be used as natural medicines. Figure 1 and Table II summarize reports about pharmacological effects such as hepatoprotective, hypoglycaemic reduction, anti-atherosclerotic and anti-atherogenic effects, anti-inflammatory and anti-nociceptive effects, anti-arthritis, antioxidant, cardiovascular and cerebrovascular effects, CNS effects, anti-infection, anti-cancer, anti-plasmodial effects, and absence of embryotoxicity (zebrafish embryo acute toxicity test).

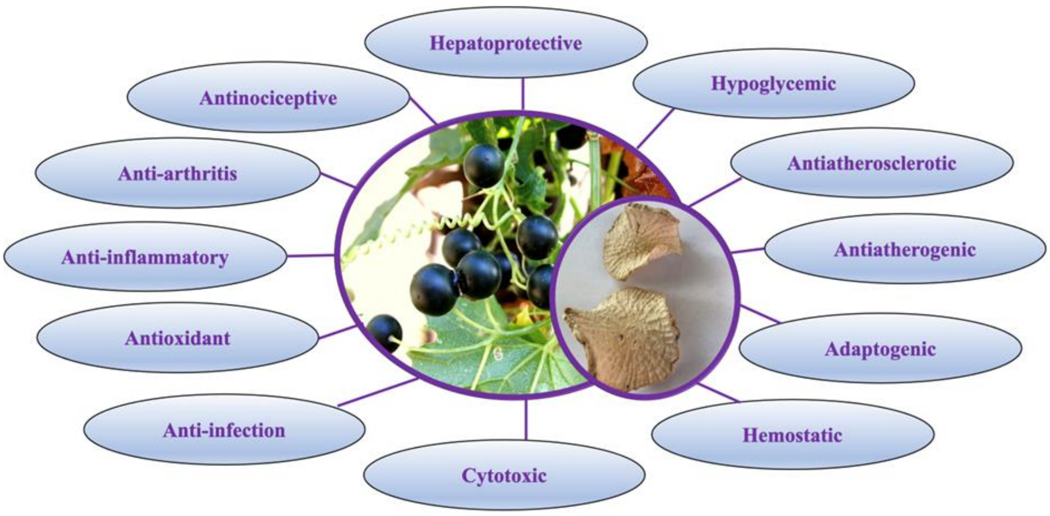

Figure 1.
The main pharmacological activity of *B. alba* roots and aerial parts

Table II

Pharmacological activities of *B. alba*

Activity	Part used	Method	Results	Phytochemicals	Reference
Hepatoprotective	Roots (ethanolic, chloroformic extracts)	CCl_4-induced hepatotoxicity	A dose of 100 mg/kg significantly restores enzyme levels and shows hepatoprotective action	Alkaloids, saponins, steroids, triterpenoids, carbohydrates, and proteins	[30]
Hypoglycaemic	Roots (no additional data; based on other publications of these authors) extract (no additional data)	Antidiabetic activity in a model of alloxan-induced diabetic rats	The rats with alloxan-induced diabetes showed an increase in the total content of phospholipids and their fractions, especially acidic phospholipids, in their blood after administration of extract at a dose of 0.5 mg/100 g of body mass. In addition, the phospholipid level returned to normal	Not defined	[35]
	Roots (trihydroxy-octadecadienoic acids (THODD))	The action and mechanism of *B. alba* on glycogen phosphorylase (a- and b-form), phosphoprotein phosphatase and hexokinase in liver and muscle tissue of white rats with diabetic alloxan metabolism.	Normalization of glycogen phosphorylase (a- and b-form), phosphoprotein phosphatase and hexokinase in liver and muscle tissue of white rats with alloxan-diabetic metabolism	THODD	[35, 74]
	Roots (trihydroxy-octadecadienoic acids)	The effect of trihydroxyoctadecadienoic acids from *B. alba* on the glucose-fatty acid cycle in alloxan-induced diabetic rats	Significantly lowered blood glucose levels and improved insulin sensitivity in diabetic rats. Reduced blood triglyceride and total cholesterol levels. The activities of key enzymes involved in the glucose-fatty acid cycle.	THODD	[74]
	Roots (THODD)	The restoration of dysfunctional lipid metabolism in alloxan-diabetic rats.	Correction of major metabolic abnormalities typical of severe diabetes mellitus; the influence of the profile of the formation of stable prostaglandins (on a dose of 0.05 mg/kg/day).	THODD	[35]
	Roots (ethanolic extracts)	Antidiabetic activity in a model of alloxan-induced diabetic rats	A significant decrease in blood glucose levels in a dose of 200 mg/kg	Not defined	[75]
Antiatherosclerotic and antiatherogenic	Roots (THODD)	Antiatherosclerotic effect *in vitro* - in cell cultures prepared from atherosclerotic plaques of human aorta. Antiatherogenic effect *in vivo* - a rabbit myointimal aortic thickening model	Anti-atherogenic effect: lowered the total cholesterol content, reduced thickness of the intima and reduced adhesion of blood cells to the surface of the arterial lumen	THODD	[34]
Anti-inflammatory	Roots (ethyl acetate extract)	Carrageenan-induced hind paw oedema model and Whittle method	Statistically significant anti-inflammatory activity, increase in capillary permeability in an acetic acid-induced mode	Phenolic compounds and cucurbitane-type triterpenoids	[76]
Antinociceptive	Roots (ethyl acetate extract)	p-benzoquinone-induced abdominal constriction test and tail flick test	Showed antinociceptive activity in the p-benzoquinone-induced writhing mouse model	Phenolic compounds and cucurbitane-type triterpenoids	[76]

Activity	Part used	Method	Results	Phytochemicals	Reference
Anti-arthritis	Roots (homoeopathic formulation in two different potencies: *Bryonia alba*-30X and *Bryonia alba*-Q)	MSU model, potassium oxonate hyperuricemia model, XDH and XOD assays	The results suggest that *B. alba* could be a potential treatment option for gouty arthritis	Not defined	[77]
Antioxidant	Roots (n-hexane, ethyl acetate and methanolic extracts)	DPPH, ABTS, total antioxidant activity (FRAP), and hydroxyl scavenging activity	Strong antioxidant activity of *B. alba* root ethyl acetate extract	Phenolics, flavonoids	[76]
	Aerial parts	DPPH, TEAC, CUPRAC, FRAP, EPR and SNPAC	Significant antioxidant capacity	Total phenol and total flavonoid content	[42]
	Leaves (methanolic extract and its isolated flavonoids)	Horseradish peroxidase (HRP)-catalyzed oxidation assay, direct myeloperoxidase (MPO) assay and cellular antioxidant assays.	By HRP-catalyzed oxidation assay- Saponarin was the most potent compound, followed by lutonarin, Isovitexin and isoorientin By MPO assay - Lutonarin proved to be the most active molecule, followed by isoorientin and isovitexin By PMA-activated -neutrophil *in vivo* method- The best inhibitory activity was obtained for isoorientin and isovitexin, followed by lutonarin and saponarin By PMA-activated - macrophage *in vitro* method- Lutonarine is the most potent, followed by isoorientine and isovitexine	Flavonoids	[46]
Effect on CNS	Roots (cucurbitacin R diglucoside (DCR))	Investigated the influence on adrenal corticosteroid production and eicosanoid biosynthesis in isolated adrenal cortical cells, blood plasma and leukocytes under stressed and stress-free conditions *in vitro* and *in vivo*.	DCR stimulates the biosynthesis and secretion of corticosterone by the rat adrenal cortex, which is evidence of the mobilization of the organism's resources. DCR prevents stress-induced changes in blood eicosanoids and moderately stimulates the adrenal cortex to adapt the organism to stress	DCR	[24]
	Roots (extract) (no additional data)	Examined expression and release of NPY and the molecular chaperone HSP72 on isolated human glial cells	A statistically significant effect for Hsp70 release	Not defined	[78]

Activity	Part used	Method	Results	Phytochemicals	Reference
	Roots (extract) (no additional data)	Investigated the molecular mechanisms of adaptogenic effect. RNA sequencing to profile gene expression alterations in T98G neuroglia cells and analyse the relevance of deregulated genes to adaptive stress-response signalling pathways using *in silico* pathway analysis software.	The extracts affected numerous genes essential to controlling adaptive homeostasis and demonstrated their ability to alter gene expression to ward off diseases caused by stress and ageing	Not defined	[79]
Anti-infection	Roots (homeopathic remedies on 30C potency)	The effect of homoeopathic remedies on the clinical characteristics of patients with COVID-19	The results showed that the most recommended homoeopathic remedies were *B. alba* (33.3%) on 30C potency.	Not detected	[80]
	Roots (homeopathic remedies on 30C potency)	The study of the effectiveness of three different homoeopathic remedies in preventing COVID-19 infection	There were significantly fewer unverified COVID-19 cases in the phosphorus group than in the other groups throughout the experiment	Not detected	[81]
	Roots (ethanolic extract)	The effect on Delta SARS-CoV-2 spike RBD protein-induced systemic inflammation in chick embryos (*Gallus gallus domesticus*)	Diluted ethanolic extract of Bryonia upregulated interferon-induced protein (IFN-α) and Interleukin 10 (IL-10) markedly. In the pre-treatment set, IFN-α, Interleukin 8 (IL-8), IL-10, and Interleukin-1β (IL-1β) were markedly decreased, while in the post-treatment set Interleukin-6 (IL-6), IL-10, IL-8, and transforming growth factor β1 (TGFβ1) were significantly decreased	Not detected	[82]
	Roots homoeopathic medicines (potencies of mother tinctures)	Examined the effect on yeast cultures	The results showed that there were no significant differences in the growth rate of *Schizosaccharomyces* pombe yeast cultures treated with different potencies of homeopathic medicines	Not detected	[83]
	Roots (homeopathic remedies on 30C potency)	A cluster-randomised, double-blind, placebo-controlled trial	Individuals given *B. alba* 30C did better than placebo in reducing the incidence of chikungunya in Kerala	-	[84]
	Roots (homeopathic remedies on 30C potency)	A randomized, double-blind, placebo-controlled prophylaxis study was conducted in a COVID-19-exposed population	Subjects who were randomized to *B. alba* signalled ($p < 0.10$) a lower incidence of laboratory-confirmed COVID-19 and a shorter period of illness, with evidence of fewer hospitalizations, than those taking a placebo	Not detected	[85]
Cytotoxic and genotoxic	Roots (cucurbitacins)	Cytotoxic activity against cell lines A549, SK-MEL-2, COLO 205, and L1210.	Cucurbitacins B, D, E, and I have high cytotoxicity, but the others are moderate.	Cucurbitacins B, D, E, I, J, K, L, and their derivatives	[6, 16, 20, 28]

Activity	Part used	Method	Results	Phytochemicals	Reference
	Roots (cucurbitacins)	The study of the binding of cucurbitacins to glucocorticoid receptors in cell-free HeLa systems and intact cells	Cucurbitacins are poor inhibitors of [^{3}H]cortisol binding to its cytosolic receptors in this cell-free system. Moreover, all cucurbitacins tested have replaced [^{3}H]cortisol bound to intact HeLa cells, a necessary step for the cytotoxic effects of these compounds	Cucurbitacins	[86]
	Roots (aqueous and methanolic extracts)	Exogenous and endogenous oxidative DNA damage in human cells using the comet assay with endonuclease III and formamido-pyrimidine DNA glycosylase and using single-cell gel electrophoresis on transformed human cells (HeLa and Caco-2) (the Comet Assay)	Extracts protect human cells from endogenous oxidative DNA damage	Not detected	[87, 88]
	Roots (aqueous and methanolic extracts)	The genotoxic activity on lymphocytes was isolated from human blood obtained from two healthy volunteers and transformed (HeLa and Caco-2) cells using single-cell gel electrophoresis (the comet assay).	No evidence of genotoxic effects of *B. alba* roots	Not detected	[89]
	Aerial parts (methanolic extract)	Cytotoxic activity against A549 (lung cancer), HeLa (cervical cancer), and WI38 (fetal lung fibroblasts) cell lines	No cellular toxicity observed	Phenolics, flavonoids	[42]
	Leaves (methanolic extract and its isolated flavonoids)	Cytotoxic activity against A549 (lung cancer), HeLa (cervical cancer), and WI38 (fetal lung fibroblasts) cell lines	No cellular toxicity observed	Flavonoids	[46]
Anti-plasmodial	Aerial parts (methanolic extract)	The anti-plasmodium falciparum activity on two plasmodium falciparum strains: 3D7 (chloroquine sensitive) and W2 (chloroquine resistant)	No cellular toxicity on the parasitic strains used observed	Phenolics, flavonoids	[42]
Acute toxicity (zebrafish embryo acute toxicity test)	Aerial parts and leaves (methanolic extract)	Acute toxicity was assessed *in vivo* by zebrafish toxicity assays: cardiovascular parameters such as heart rate and blood circulation, dermatological parameters and motility, and morphological changes were assessed for zebrafish larvae	No significant changes in these parameters were observed	Phenolics, flavonoids	[42, 46]

Activity	Part used	Method	Results	Phytochemicals	Reference
Haemostatic	Roots (tincture and its hydrogen residue after evaporation)	model 1- linear incised wound and model 2- parenchymal bleeding in white rats (local application)	A significant hemostatic effect was shown by both tincture and its hydrogen residue when applied topically to the wound surface of the liver, reducing the time of parenchymal bleeding.	Saponins (cucurbitacins), alkaloids, sugars	[90]

Hepatoprotective activity

Manvi *et al.* [30] investigated the hepatoprotective effects of chloroform and ethanol extracts of *B. alba* roots from two different origins (Indian and European) against CCl_4-induced hepatotoxicity. The mechanism of this method is based on the increase in serum marker enzymes, in particular serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, total bilirubin, and alkaline phosphatase in liver damage. The control group was the silymarin treatment. This study was also supported by histopathological studies. The study shows a significant restoration of these enzyme levels when administered with the roots extract, along with silymarin at a dose of 100 mg/kg. The author suggests that the extract's reversal of elevated serum enzymes in CCl_4-induced liver damage might be due to the prevention of leakage of intracellular enzymes through its membrane-stabilizing activity. It is also reported that chloroform extract is rich in alkaloids steroids and triterpenoids. The ethanolic extract is rich in alkaloids, saponins, triterpenoids, carbohydrates, and proteins.

Hypoglycaemic activity

Vartanian *et al*. [35] evaluated the effects of *B. alba* extract on diabetic rats. The methods used in the study include inducing diabetes in rats with alloxan, administering *B. alba* extract at a dose of 0.5 mg/100 g body mass to diabetic rats, and analysing blood samples from rats to determine the qualitative and quantitative changes in the content general and individual phospholipids and their fractions. The rats' blood with alloxan-induced diabetes had an increase in the total content of phospholipids and their fractions, especially acidic phospholipids. While neutral phospholipids increase incomparably lesser degree. This is expressed in a decrease in the ratio of the sum of neutral phospholipids to the sum of acidic phospholipids. However, after administration of *B. alba* extract to diabetic rats, the level of phospholipids returned to normal.

The hypoglycaemic activity of fatty acids (particularly trihydroxyoctadecadienoic acids) from *B. alba* roots and the mechanism of their influence on the normalization of glycogen phosphorylase (a- and b-form), phosphoprotein phosphatase and hexokinase in liver and muscle tissue of white rats with alloxan diabetic metabolism were all studied [33].

Vartanian *et al.* [74] studied the effect of trihydroxyoctadecadienoic acids from *B. alba* on the glucose-fatty acid cycle in alloxan-induced diabetic rats. The rats were divided into four groups: normal controls, diabetic controls, trihydroxyoctadecadienoic acids-treated diabetic rats, and diabetic rats treated with glibenclamide (a standard antidiabetic drug). Blood sugar levels, insulin levels, and lipid profiles were measured in all groups. In addition, the glucose-fatty acid cycle was assessed by measuring the activities of the key enzymes involved in the cycle. The results showed that treatment with trihydroxyoctadecadienoic acids from *B. alba* significantly lowered blood glucose levels and improved insulin sensitivity in diabetic rats. Trihydroxyoctadecadienoic acids also reduced blood triglyceride and total cholesterol levels. The activities of key enzymes involved in the glucose-fatty acid cycle were also enhanced by treatment with trihydroxyoctadecadienoic acids. These results suggest that trihydroxyoctadecadienoic acids from *B. alba* may have potential as a natural antidiabetic.

Karageuzyan *et al.* [35] found that trihydroxyoctadecadienoic acids derived from the roots of *B. alba*. (0.05 mg/kg/day for 15 days, i.m.) restored dysfunctional lipid metabolism in rats with alloxan diabetes. The mechanism of action is that diabetes was associated with an increase in the total amount of non-esterified fatty acids in the blood together with a decrease in the total amount of non-esterified fatty acids and triglycerides in muscle and adipose tissue, together with a noticeable change in the distribution of phospholipid fatty acids of muscle membranes, including an increase in short-chain fatty acid content and a decrease in arachidonate content. Treatment with trihydroxyoctadecadienoic acid effectively reversed all these metabolic changes caused by diabetes, except decreased muscle triglycerides, which were not reversed. Furthermore, in an in vitro experiment with rat neutrophils, a mixture of four diastereoisomeric trihydroxyoctadecadienoic acids at concentrations of 5 to 50 µg/mL did not affect 5-lipoxygenase activity or granular enzyme secretion but reduced the formation of thromboxane B_2 in a dose-dependent manner, increasing prostaglandin E_2 release.

Another study shows that ethanolic extracts of *B. alba* root (200 mg/kg) administered orally for 7 days caused a significant decrease in blood glucose levels in the rat model of alloxan-induced diabetes [75].

Antiatherosclerotic and antiatherogenic activities

Orekhov *et al*. [34] evaluated the antiatherosclerotic and antiatherogenic activities of isolated mixtures of trihydroxyoctadecadienoic acids from *B. alba* roots. The anti-atherosclerotic activities were examined in cell cultures obtained from atherosclerotic plaques of the human aorta. Trihydroxyoctadecadienoic acids in the concentration range of 10^{-8} - 10^{-4} M lowered the total cholesterol content more than nifedipine and inhibited the incorporation of [^{3}H]-thymidine into the cultured cells. In addition, the anti-atherogenic activities of trihydroxyoctadecadienoic acids from *B. alba* roots in deendothelialized rabbit aorta were investigated. It showed an anti-atherogenic effect due to reduced thickness of the intima and reduced adhesion of blood cells to the surface of the vascular lumen.

Anti-inflammatory and antinociceptive activities

Ilhan *et al*. [76] determined the anti-inflammatory activities of *B. alba* roots in different extracts with n-hexane, ethyl acetate and methanol. The anti-inflammatory activity of the extract in mice was evaluated using a carrageenan-induced hind paw oedema model and the Whittle method. In the inflammation model, rats were injected with carrageenan in their paws and the volume of oedema was measured every 90 min for 6 h. Meanwhile, the Whittle method used acetic acid to increase vascular permeability in mice. Ethyl acetate extract from *B. alba* roots showed statistically significant anti-inflammatory activity in a carrageenan-induced hind paw oedema model and an increase in capillary permeability in an acetic acid-induced model.

Ilhan *et al*. [76] also examined the antinociceptive activity of *B. alba* root extracts using the p-benzoquinone-induced abdominal constriction test. It was performed on mice to which 0.1 mL of a 2.5% (w/v) p-benzoquinone solution in distilled water was intraperitoneally administered 60 min after oral administration of a test sample. The ethyl acetate extract showed antinociceptive activity in the p-benzoquinone-induced writhing mouse model. In this study, the highest biological effect was associated with an increase in phytochemical concentrations such as cucurbitacins, lectins, flavonoids, and lipids in ethyl acetate extract from *B. alba* roots.

Anti-arthritis activity

Yashwanth *et al*. [77] evaluated the efficacy of the homoeopathic formulation of *Bryonia alba* in treating several chemically engineered gouty arthritis models in rats. The drugs, in two different potencies (*Bryonia alba*-30X and *Bryonia alba*-Q), were studied in several models of gouty arthritis. In the first model, the drug's ability to reduce symptoms was evaluated by inducing inflammation with monosodium urate (MSU) and comparing the results to an indomethacin control. In the second model, hyperuricemia was induced using potassium oxonate, and the ability of the formulation to lower elevated serum uric acid was examined. To determine whether the drug suppresses these enzymes compared to allopurinol as a reference, xanthine dehydrogenase (XDH) and xanthine oxidoreductase (XOD) assays were performed. The results showed that the homoeopathic formulation of *Bryonia alba* was effective in reducing inflammation in the MSU-induced gouty arthritis model in rats. The drug was also able to reduce elevated serum uric acid levels in the potassium oxonate-induced hyperuricemia model. The XDH and XOD assays showed that the drug inhibits these enzymes involved in uric acid metabolism. The results suggest that *B. alba* could be a potential treatment option for gouty arthritis.

Antioxidant activity

Ilhan *et al.* [76] investigated the antioxidant activity of different *B. alba* root extracts (n-hexane, ethyl acetate and methanol). Antioxidant activity was measured using DPPH assay (2,2-diphenyl-1-picrylhydrazyl), ABTS assay ([2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonate)] radical-scavenging), total antioxidant activity (FRAP assay-ferric reduction ability of plasma), and hydroxyl scavenging activity. This research showed that ethyl acetate extract from *B. alba* root had potent DPPH, ABTS, and hydroxyl scavenger activities of 82.6%, 87.1%, and 26.5%, respectively. Furthermore, the overall antioxidant activity of *B. alba* root ethyl acetate extract was high at 66.3 μM TE/g d.w, compared to the reference, n-hexane and MeOH of *B. alba* root extract, respectively. In this study, powerful biological activities were linked to its high content of phenols and flavonoids.

Ielciu *et al.* [42] evaluated the antioxidant activity of aerial parts of *B. alba* using different methods including DPPH assay, TEAC assay (Trolox equivalent antioxidant capacity), CUPRAC assay (cupric reduction antioxidant capacity), FRAP assay (ferric reduction ability of plasma), SNPAC assay (silver nanoparticle antioxidant capacity), and EPR assay (electron paramagnetic resonance method). The aerial parts of the species showed significant antioxidant capacity with DPPH (IC_{50} μg/mL) - 99.8 ± 0.92 CUPRAC (μM TE/100 mL) - 238 ± 2.24, FRAP (μM TE/100 mL) - 217 ± 2.45, TEAC (IC_{50} μg/mL) - 19.9 ± 0.89, SNPAC (μM TE/100 mL) -

427 ± 2.46, EPR (Integral intensity) - 401.96 ± 2.72). This is evident from the results of quantification of total phenol and total flavonoid content and correlates strongly with the results of antioxidant activity assays.

In a recent study by Ielciu *et al*. [46] the antioxidant activity of leaf extract and its isolated flavonoids was evaluated using a horseradish peroxidase (HRP)-catalysed oxidation assay, a direct myeloperoxidase (MPO) assay, and cellular antioxidant assays. The HRP and MPO methods demonstrate the inhibitory effect of tested samples on the oxidation of a chemiluminescence (CL) probe (L012) as a reducing substrate which is catalysed by the HRP enzyme, but also on MPO, using Amplex Red as a proven reducing substrate, in the presence of H_2O_2. Meanwhile, cellular antioxidant assays examined the effects of the tested samples on the total reactive oxygen species (ROS) produced by PMA (phorbol-12-myristate-13-acetate) upon neutrophil and macrophage activation. Tested concentrations were between 2 and 100 µg/mL. The HRP-catalysed oxidation assay showed that saponarin was the most potent compound, followed by lutonarin, isovitexin, and isoorientin. Meanwhile, the direct MPO assay showed that the inhibition of the enzyme is significant for most of the samples tested and the inhibition is dose-dependent. Lutonarin proved to be the most active molecule, followed by isoorientin and isovitexin. In addition, the effects on total ROS produced by the PMA-activated neutrophil *in vivo* method showed that the best inhibitory activity was obtained for isoorientin and isovitexin, followed by lutonarin and saponarin. Furthermore, the effect of crude leaf extract and its isolated flavonoids on the inhibition of macrophage-produced ROS when activated by PMA showed dose-dependent inhibition. Moreover, the samples tested were more potent than the crude extract, with marked activity for lutonarine, followed by isoorientine and isovitexine.

Effects on CNS

Panossian *et al.* [24] investigated the influence of cucurbitacin R diglucoside (DCR), one of the active components in *B. alba*, on adrenal corticosteroid production and eicosanoid biosynthesis in isolated adrenal cortical cells, blood plasma, and leukocytes under stressed and stress-free conditions *in vitro* and *in vivo*. For this study, two groups of 20-25 animals were used. Before immobilization, the rats were injected with 0.1 mg/kg of DCR dissolved in isotonic saline in the dorsal neck region. The results showed that DCR stimulates the biosynthesis and secretion of corticosterone by the rat adrenal cortex, which is evidence of the mobilization of the organism's resources. It also suggested that DCR prevents stress-induced changes in eicosanoids in the blood and moderately stimulates the adrenal cortex to adapt the organism to stress.

Asea *et al*. [78] examined the effect of several plant extracts (n = 23, including *B. alba*) on biomarkers (neuropeptide Y (NPY) and/or molecular chaperone Hsp72 from isolated human neuroglial cells of adaptogenic activity. Selected validated adaptogens, partially validated adaptogens, claimed but rarely validated adaptogens, and other plant extracts that affect the neuroendocrine and immunological systems but have never been considered adaptogens were among the extracts in this group. High-throughput ELISA techniques were used to measure adaptogenic activity. The results showed that tonics and stimulants had no discernible effect on NPY in this *in vitro* test, while the activating effects of *B. alba* were only significant for Hsp70. These studies were subsequently verified using primary human neurons, which showed that adaptogens activate both NPY and Hsp70 release, while non-adaptogens tested were inactive in the NPY assay and inhibited Hsp70 release.

Panossian *et al*. [79] investigated the molecular mechanisms of several adaptogenic plants, including *B. alba*, which are commonly used to treat stress- and age-related diseases. To better understand how adaptogens function at the molecular level, *in silico* pathway analysis software was used to assess the importance of unregulated genes for adaptive stress response signalling networks. After treatment with adaptogens, T98G neuroglial cells were subjected to RNA sequencing to profile changes in gene expression. The results showed the effects of different adaptogenic herbal extracts in brain cell cultures on the genome as a whole. In this study, the constant activation of ASRSPs by adaptogens in T98G neuroglial cells was underscored. The extracts affected numerous genes essential to controlling adaptive homeostasis and demonstrated their ability to alter gene expression to ward off diseases caused by stress and ageing. Overall, this study provides readers with a thorough understanding of the molecular processes through which adaptogens exert their stress-reducing benefits.

Anti-infection activity

Hagelberg *et al.* [80] examined the effect of homoeopathic medicines on yeast cultures. The growth of the yeast cultures was determined by measuring the optical density at 600 nm (OD600) using a spectrophotometer. The results showed that there were no significant differences in the growth rate of Schizosaccharomyces pombe yeast cultures treated with different potencies of homoeopathic medicines (*Sulphur, Arnica montana, Chamomilla,* *Bryonia alba*, *Euphrasia officinalis and Pulsatilla*) compared to the controls.

Jethani *et al.* [81] pointed out homoeopathic remedies based on the clinical characteristics of patients with COVID-19 in India. Between April 29 and June 17, 2020, confirmed COVID-19 patients for this study were treated with both conventional and homoeopathic methods at a COVID health centre in New Delhi. The patients were divided into groups with mild, moderate, or severe disease. The study included 178 patients with mild symptoms, 80 patients with moderate symptoms, and none with severe symptoms because they were sent to tertiary care on ventilator support. The results showed that the most commonly recommended homoeopathic remedies were *B. alba* (33.3%), *Arsenicum album* (18.1%), *Pulsatilla nigricans* (13.8%), *Nux vomica* (8%), *Rhus toxicodendron* (7, 2%) and *Gelsemium sempervirens* (5.8%) all at 30C potency.

In Mukherjee *et al*. [82] the effectiveness of three different homoeopathic remedies in preventing COVID-19 infection was compared with a placebo. A sample of 20,000 members of the general public in Kolkata's Tangra district was randomly assigned one of three homoeopathic remedies (*Bryonia alba* 30cH, *Gelsemium sempervirens* 30cH, or Phosphorus 30cH) or a similar-looking placebo for three days (for children) or six days (for adults). As a positive control, all subjects received 500 mg of ascorbic acid (vitamin C) for six days. The ages of the participants ranged from 5 to 75 years. Accordingly, there were significantly fewer unverified COVID-19 cases in the phosphorus group than in the other groups throughout the experiment.

Nair *et al*. [83] conducted a study in Kerala for chikungunya prevention during the epidemic outbreak in August/September 2007 in three panchayats from two districts. A cluster-randomized, double-blind, placebo-controlled study of *Bryonia alba* 30C/placebo was randomly administered to 167 clusters (*Bryonia alba* 30C=84 clusters; placebo = 83 clusters), from which data from 158 clusters (*Bryonia alba* 30C=82 clusters; placebo = 76 clusters) were analysed. A weekly check was carried out for 35 days. The results showed that 2,525 of 19,750 people in the *Bryonia alba* 30C group had chikungunya, compared to 2,919 of 18,479 in the placebo group. Using cluster analysis, a significant difference was found between the two groups [rate ratio = 0.76 (95% CI 0.14 - 5.57), p-value = 0.03]. The results showed a relative risk reduction of 19.76% with *Bryonia alba* 30C compared to placebo.

In another study, the effect of a diluted ethanolic extract of *B. alba* on Delta SARS-CoV-2 spike RBD protein-induced systemic inflammation in chick embryos (*Gallus gallus domesticus*) was examined. Delta SARS-CoV-2 spike RBD recombinant protein was inoculated into 14-day-old chick embryos (*Gallus gallus domesticus*) along with control, pre- and post-treatment sets of diluted Bryonia extract. After 48 h, allantoic fluids were collected and stored at 20°C for the study of various cytokines. Histological changes in the liver were also examined in each animal. The results showed that the diluted ethanolic extract of Bryonia upregulated interferon-induced protein (IFN-α) and Interleukin 10 (IL-10) markedly. In the pre-treatment set, IFN-α, Interleukin 8 (IL-8), IL-10, and Interleukin-1β (IL-1β) were markedly decreased, while in the post-treatment set Interleukin-6 (IL-6), IL-10, IL-8, and transforming growth factor β1 (TGFβ1) were significantly decreased, with a tendency of more anti-inflammatory surge than pro-inflammatory cytokines. The experiment indicated an immunomodulatory role of diluted ethanolic *B. alba* extract particularly in the post-treatment set, decreasing pro-inflammatory cytokines with a beneficial effect [84].

Talele *et al*. [85] examined the effects of various drugs on a population exposed to COVID-19 in a quarantine facility in Bombay, India. A six-group, randomized, double-blind, placebo-controlled prophylactic study was conducted. *Arsenicum album* 30c, *Bryonia alba* 30c, a mixture of these two (*Arsenicum album* 30c, *Bryonia alba* 30c, *Gelsemium sempervirens* 30c, and *Influenzinum* 30c), the coronavirus nosode CVN01 30c, Camphora 1M, or a placebo were administered to each group. Six tablets were taken twice a day for three days. Testing recruitment and retention in this closed environment was the main outcome metric used. The number of people who tested positive for COVID-19 after showing signs of the disease, the number of patients hospitalized and the length of days to recovery were secondary findings. The study had successful retention and recruitment rates. 2,343 of the 4,497 people quarantined asked to participate; 2,294 were accepted and 2,233 completed the study (49.7% recruitment, 97.3% retention). Randomized subjects who received either *Bryonia alba* or the CVN01 nosode indicated potential efficacy in preventing COVID-19.

Cytotoxic activity

Previous research has highlighted the importance of cucurbitacins isolated from *B. alba* roots, particularly cucurbitacins B, D, E, I, J, K, L, and their derivatives, which have cytotoxic activity against cell lines A549, SK-MEL-2, COLO 205, and L1210 [6, 16, 20, 28].

Witkowski *et al*. [86] studied the binding of cucurbitacins isolated from *B. alba* to glucocorticoid receptors in cell-free HeLa systems and intact cells through competition with [^{3}H]cortisol. Inhibition of

[^{3}H]cortisol binding to its specific cytoplasmic receptors by three cucurbitacins (cucurbitacins B, I and THI) was a concentration-dependent process, while cucurbitacin J had no effect. Cucurbitacins are poor inhibitors of [^{3}H]cortisol binding to its cytosolic receptors in this cell-free system. Moreover, all cucurbitacins tested have replaced [^{3}H]cortisol bound to intact HeLa cells, a necessary step for the cytotoxic effects of these compounds. In addition, the influence of temperature on the inhibitory effect of cucurbitacin on [^{3}H]-cortisol binding was investigated.

The effect of aqueous and methanolic extracts of the Loshtak preparation (purified *Bryonia alba* roots) on exogenous and endogenous oxidative DNA damage was studied in human cells using the comet test with endonuclease III and formamidopyrimidine DNA glycosylase [87]. Nersesyan *et al*. [88] analysed the effect of the aqueous and methanolic extracts of *B. alba* on external and endogenous oxidative DNA damage using single-cell gel electrophoresis on transformed human cells (HeLa (epithelial cells) and Caco-2 (colon carcinoma cells)) (the Comet Assay). Exogenous oxidative DNA damage caused by H_2O_2 cannot be prevented by Loshtak extracts, while endogenous oxidative DNA damage can be prevented. The Loshtak preparation protects human cells from endogenous oxidative DNA damage [87, 88].

The genotoxic activity of aqueous and methanolic extracts from *B. alba* roots was investigated. The genotoxic activity was tested on lymphocytes isolated from human blood obtained from two healthy volunteers. As with the genotoxic activity performed on transformed HeLa and Caco-2, the lymphocytes were grown in different media. DNA breaks were detected using an adaptation of the single-cell gel electrophoresis method (the Comet Assay). The results obtained showed no evidence of genotoxic effects of *B. alba* roots [89].

In addition, the cytotoxicity of aerial parts of *B. alba* against the cell lines A549 (lung cancer), HeLa (cervical cancer), and WI38 (foetal lung fibroblasts) was investigated. Sample concentrations ranged from 2 to 100 µg/mL. Cell viability was determined after 48 hours by adding WST-1 tetrazolium salt and measuring absorbances at 450 nm on a multiwell scanner. No cellular toxicity was observed in the samples tested at concentrations of 100 µg/mL or less, either in human cancer cell lines or in healthy human cell lines [42].

According to a recent study, *B. alba* leaf extract has no cellular toxicity (IC_{50}>50) against cell lines A549 (lung cancer), HeLa (cervical cancer), and WI38 (foetal lung fibroblasts) [46].

Anti-plasmodial activity

The anti-plasmodium falciparum activity of aerial parts of *B. alba* on two *Plasmodium falciparum* strains - 3D7 (chloroquine sensitive) and W2 (chloroquine-resistant) -- was reported by Ielciu *et al*. [42]. The concentrations of the tested samples ranged from 0.8 to 100 µg/mL. The activity of plasmodial lactate dehydrogenase (pLDH) at 630 nm was used to measure the inhibition of parasite growth. The samples tested did not show any cellular toxicity *in vitro*. The extract contained phenolics and flavonoids.

Acute toxicity (zebrafish embryo toxicity assay)

Ielciu *et al*. [42] tested methanol extract rich in phenolic compounds from *B. alba* aerial parts for toxicity using zebrafish toxicity assays. Fertilized zebrafish eggs were used for this method. They were incubated at 28°C and kept on a 14-h-day/10-h-night cycle throughout the experiment. The chorions of the larvae were removed. The larvae medium containing the crude extract (concentrations ranging from 0.1 to 100 µg/mL) was changed once a day. At 24 (hours post fertilisation) hpf, 48 hpf, and 72 hpf, various parameters were measured by comparing exposed embryos to controls. Cardiovascular parameters such as heart rate and blood circulation were assessed, as well as dermatological parameters and motility. At the same time, morphological changes in embryo development were observed. During the experiment, no significant changes in these parameters were observed for the tested samples.

Another study by Ielciu *et al*. [46] using the zebrafish larvae model and *B. alba* leaves extract found no changes within 72 h in cardiovascular (heart rate, blood circulation), dermatological, motility, or morphological aspects.

Haemostatic activity

Karpiuk *et al*. [90] carried out a study of haemostatic effects for the tincture of *B. alba* roots (60% ethanol) and its hydrogen residue after evaporation (to reverse the caustic effect of alcohol) on white rats using two models: linear incised wound and parenchymal bleeding. Stoppage of the bleeding was determined by topical application of the extract. The haemostatic effect of the tincture was determined by the duration of bleeding (according to the Duque method), observed after inflicting a cut wound on the animals, and was recorded using a stopwatch. A significant haemostatic effect was shown by both tincture and its hydrogen residue when applied topically to the wound surface of the liver, reducing the time of parenchymal bleeding. The two effects were nearly identical. It was mentioned that cucurbitacins, alkaloids and sugars were present in tincture.

Side effects

Poisonous compounds of *B. alba* roots are believed to be cytotoxins and microtubule modulators. Nausea, vomiting, diarrhoea with blood, inflammation of the kidneys, severe colic with gastrointestinal spasm, tachycardia, CNS lesions, and respiratory arrest are all symptoms of overdose [21, 27].

It has been reported about the side effects of the Bryonia extract (Loshtak 100 mg tablets). The following side effects have been noticed after excessive intake (more than 2 tablets per day): diarrhoea, drowsiness, tachycardia, and hyperexcitability [23].

This review gives summaries of reported biological activity, side effects, and probable toxicity, involving numerous phytochemical constituents of *B. alba*. This plant species was chosen for this thorough literature search because it is one of the most important and well-known members of the genus *Bryonia*; it is rich in cucurbitacins, a very important class of compounds responsible for a broad-spectrum range of biological activities including cytotoxic, antitumor, hepatoprotective, anti-inflammatory, antibacterial, anthelmintic, cardiovascular, and antidiabetic effects. In addition, some of the cucurbitacins have anti-inflammatory or analgesic effects. Several studies have also shown a synergistic interaction between cucurbitacins and known chemotherapeutic agents such as doxorubicin and gemcitabine. *B. alba* is widely used in traditional medicine as an anti-inflammatory, antipyretic, antibacterial, diuretic, analgesic, laxative, haemostatic, anxiolytic, local irritant, CNS suppressor, and muscle relaxant, as well as in the treatment of rheumatism, gastroenterological disorders, neuropsychological diseases, pneumonia, measles, and bronchitis. Our review covers various phytocomponents covering different chemical classes, including triterpenes, phytosterols, lipids, fatty acids, amino acids, polysaccharides, macro- and microelements, flavonoids, and phenols. The observed phytoingredients have been correlated with a variety of biological functions. The abundance of alkaloids, saponins, steroids, triterpenoids, carbohydrates, and proteins in *B. alba* was mainly responsible for the hepatoprotective effect. The hypoglycemic, antiatherosclerotic, and antiatherogenic properties of trihydroxyoctadecadienoic acids have been demonstrated. In addition, cucurbitan-type triterpenoids and phenolic compounds exhibited anti-inflammatory and antinociceptive properties. The content of flavonoids and phenols showed an antioxidant effect. To help the body adapt to stress, cucurbitacin R diglucoside reduces stress-related changes in eicosanoids in the blood and slightly activates the adrenal cortex, which explains their activity in the central nervous system. The cytotoxic properties of cucurbitacins B, D, E, I, J, K and L have been demonstrated.

The obtained data indicate the prospect of using *B. alba* for the preparation of medicinal products with different activities. Also, we can outline the need for further studies of the active components and the establishment of the dependence between the composition and the pharmacological activity.

Conclusions and prospects

B. alba has been the topic of phytochemical and pharmacological study over the past over than 50 years, and it is well-known in homoeopathic practice. Literature analysis shows that *B. alba* is used in herbal medicine worldwide for a variety of well-known medicinal purposes. Hepatoprotective, hypoglycaemic, antiatherosclerosis, antiatherogenic, anti-inflammatory, antinociceptive, anti-arthritis, antioxidant, adaptogenic, anti-infection, anticancer, and anti-plasmodial effects have all been discovered for roots and aerial parts of *B. alba*. The roots and aerial parts of *B. alba* have been found to exhibit no genotoxic or embryotoxic effects on zebrafish embryos. Different phytochemicals such as alkaloids, saponins, steroids, triterpenoids, carbohydrates, proteins, and lipids are the primary components of *B. alba* MPM.

While the therapeutic benefits of *B. alba* have been recognized, the exact phytochemical and pharmacological mechanisms responsible for these effects are still not fully understood. Despite the existing evidence supporting the potential health benefits, further in-depth research is necessary to establish a clearer link between the medicinal properties of *B. alba* and its specific phytochemical components. By conducting more extensive studies, we can gain a deeper understanding of the therapeutic potential of *B. alba* and unlock its full range of health benefits for human well-being.

Similar reviews of the literature continue to be relevant and are conducted to gain a deeper understanding of the state of plant studies and the urgent need for further research. Detailed pharmacokinetic, *in vivo*, and clinical trial investigations utilizing chemicals derived from *B. alba*, particularly in extracts from the plant parts, are still needed.

Conflict of interest

The authors declare no conflict of interest.

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