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A Comprehensive Review on Traditional Uses, Chemical Constituents, and Diverse Pharmacological Importance of the Genus *Breynia*

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Abstract: The genus *Breynia* (family Phyllanthaceae) is widely distributed in Australia, Vietnam, Malaysia, and some regions of India. Traditionally, species of this genus were used to treat various disorders, like skin diseases, pain, cough, tonsillitis, dysentery, and headache. Various studies about this genus are available, but reviews highlighting its pharmacology and phytochemistry are inadequate. This review highlights the pharmacology, phytochemistry, and chemotaxonomic classification of the phytochemicals of ten species of the genus *Breynia*. About 90 compounds have been isolated from *Breynia* species, including glycosides, flavonoids, terpenoids, steroids, alkaloids, lignans, phenolic compounds, and catechins. Their structure and presence in each species are presented in tabular form. In pharmacological medicines, the crude extracts and metabolites of the genus *Breynia* have been found to exhibit diverse biological activity, including, antioxidant, antimicrobial, antidiabetic, anti-inflammatory, anticancer, antiviral, and activity against various blood disorders. Few isolated compounds show enzyme inhibitory activity (tyrosinase, xanthine oxidase, and elastase inhibition).

Keywords: *Breynia*; Phyllanthaceae; chemotaxonomic classification; phenolic compounds; glycosides; pharmacology.

1. Introduction

Natural products which are derived from plants play an important role in the maintenance of human health. In ancient times, plants were the main source of medicines. Plant-derived medicinal products have negligible side effects on human health. Medicinal plants are the main source of various bioactive compounds having diverse therapeutic properties. The therapeutic effects interrelated with medicinal plants include antiviral, anti-inflammatory, antidiabetic, antitumor, antioxidant, and analgesic properties [1].

Breynia is a plant genus in the family Phyllanthaceae which is one of the five segregates of Euphorbiaceae sensu lato, an angiosperm phylogeny group. This family contains about 2000 species in 59 presently accepted genera, 10 tribes, and 2 subfamilies [2]. Most of the plants in the Phyllanthaceae family are trees, shrubs, or herbs, some of them are climbers, and one species is aquatic [3]. The

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species of the genus *Breynia* are mostly found in Australia, Vietnam, Malaysia, and some regions of India. It is not a native plant of Pakistan but four species are grown in Pakistan, in Karachi and Lahore.

The genus *Breynia* is comprised of evergreen trees and shrubs. They grow to a small size, known as shrubs, and have colourful leaves; mostly their leaves are flattened. The flowers are in small size. *Breynia* species are monoecious. Their leaves are simple, distichous and petioles are short in size. In flowers, the calyx is six-lobed, petals and discs are absent. The fruit is a small fleshy capsule, about 5 mm wide, usually red in colour. The seed is triangular in transverse section, black in colour, and covered with a thin aril. This plant is mostly grown in warmer areas; the soil must be humus-rich. Fifty species of *Breynia* are known in different regions, of which 30 species are found in the above-mentioned regions [4]. The most common species of *Breynia* are *B. racemosa*, *B. vitis-idaea*, *B. disticha*, *B. discigera*, *B. fruticosa*, *B. rostrata*, *B. retusa*, *B. androgyna* (*Sauropus androgynus*), and *B. officinalis*.

2. Traditional Uses

The plants in this genus are mostly used for medicinal purposes, especially their leaves [5]. Traditionally, the leaves of *B. discigera* are used for the treatment of kidney disorders and *B. racemosa* with turmeric is used for various skin disorders [6]. In the Philippines, the bark of *B. vitis-idaea* is used as an astringent to stop haemorrhages, and its dried leaves as a treatment for tonsillitis and skin diseases. The leaves of *B. vestita* are rubbed over the body for the treatment of malaria and other fevers, also being used for the treatment of dysentery, cough, and headache. In various regions, their young leaves are used as a vegetable [7]. *B. glauca* and *B. fruticosa* are used as anti-inflammatory agents [7, 8]. Traditionally in Indonesia, *B. androgyna* is used as a lactation enhancer, due to the presence of vitamin A (vitamin A synthesizes retinol, and retinol reacts with fatty acids (triggering release of the hormone prolactin)), increasing the production of breast milk [9]. *B. oblongifolia* is used as an antiviral [10], and many other species are used for different medicinal purposes.

3. Phytochemical Studies

Phytochemicals are biologically active compounds, found naturally in plants, protect plants from environmental hazards, and also provide colour, aroma, and flavour to plants. These chemicals provide different health benefits to humans when their dietary intake is significant. Phytochemicals are majorly used for disease prevention, as anticancer, anti-inflammatory, antimicrobial, and antidiabetic agents, and work as various immunity-potentiating agents. They are accumulated in different parts of plants, such as in roots, stems, leaves, flowers, seeds, and fruits [11]. Compounds **1–90** were isolated from species of the genus *Breynia* (Table 1, Table S1 in supporting information). Commonly, glycosides are the major constituents of this genus. Many alkaloids, terpenoids, lignin, steroids, catechins, aromatic ketones, nucleosides, tannins, and aromatic heterocyclic compounds are reported in this genus.

Glycosidal compounds isolated from genus *Breynia*: among the reported compounds, 13–80 are glycosides. Flavonoidal, sulphur-containing spiroacetal, ionol, phenolic, megastigmane, isoprenoid, spiroketal, and simple glycosides were isolated from *B. fruticosa* (whole plant extract), *B. officinalis* (leaf extract), *B. rostrata* (leaf extract), *B. glauca* (leaf extract), *B. androgyna* (leaf extract), and *B. retusa* (leaf extract) (Table 1).

Flavonoids, including compounds **10–12**, were isolated from *B. retusa* (leaf and fruit extract), *B. glauca* (leaf extract), and *B. fruticosa* (leaf extract).

Terpenoids, including compounds **87–89**, were isolated from *B. rostrata* (leaf extract) and *B. fruticosa* (leaf extract).

Alkaloids: there are a total of five alkaloids, separated from *B. coronata* (leaf extract), numbered **1–5**; three of them (**2–4**) are the structural derivative of **1**. In this genus, alkaloids are reported in less quantity as compared to glycosides and flavonoids.

Catechins, isolated from *B. retusa* (leaf, fruit, and stem bark extract) are numbered **7–9** in Table 1.

Aromatic ketones: only one aromatic ketone compound was isolated from *B. fruticosa* (leaf extract), numbered 6 in Table 1.

Lignins (phenylpropane units joined together with β, β-bonds) and neolignan (phenylpropane units linked together with other carbon–carbon bonds) are phenolic compounds. Among the reported compounds, **81** was lignin, and **82–84** were neolignans, isolated from *B. fruticosa* (leaf extract), *B. rostrata* (leaf extract), and *B. androgyna* (leaf extract).

Steroidal compounds: isolated from *B. androgyna* (leaf extract), numbered **85** and **86** in Table 1.

Tannins: only one compound, numbered **90** was isolated from *B. rostrata* (leaf extract).

All these mentioned compounds were isolated and detected by ^{1}H-NMR, ^{13}C-NMR, MS, LC-MS, HPLC, LC-DAD-MSn, a two-column LC method, FTIR, and IR spectroscopy. The extraction of roots, leaves, bark, stem, flowers, and seeds of species of the genus *Breynia* was done with ethanol (EtOH), methanol (MeOH), chloroform ($CHCl_3$), n-butanol (n-BuOH), ethyl acetate (EtOAc), petrol, dichloromethane (CH_2Cl_2), dimethyl sulphoxide (DMSO), and water (H_2O).

This mentioned data revealed the chemotaxonomic classification of phytochemicals present in ten species of the genus *Breynia*.

3. Pharmacological Activity

The pharmacological or biological activity of a plant extract describes its beneficial or adverse effect on human health [42]. The genus *Breynia* has medicinal importance due to the presence of secondary metabolites such as glycosides, terpenoids, alkaloids, lignins, steroids, nucleosides, tannins, and phenolic compounds. The biological activities of various species of the genus *Breynia* are highlighted below.

Antimicrobial activity is activity that inhibits the growth of microbes or may destroy microbial colonies. The EtOH extract of *B. retusa* leaves shows effective results against *Salmonella* Typhimurium, *E. coli*, and *Enterobacter aerogenes* and is less effective against *Micrococcus luteus*. Also, it is more effective against *Trichophyton rubrum*, *Aspergillus niger*, and *Penicillium* sp. and less effective against *Cryptococcus* sp. fungi. This plant is rich in tannins (best for wound healing). This activity is highly sensitive with a high concentration [43]. Petrol, CH_2Cl_2, BuOH, EtOAc, and MeOH extracts of *B. cernua* stem, leaves, root bark, and heartwood show broad-spectrum antimicrobial activity but MeOH extract of root bark shows the best activity against microbes, and CH_2Cl_2 extract of stem bark shows good activity against all fungi [44]. MeOH and EtOH extracts of *B. androgyna* leaves show significant antibacterial activity against *Bacillus cereus*, *Proteus vulgaris*, *Staphylococcus aureus*, *E. coli*, *Klebsiella pneumonia*, and Gram-positive bacteria. They also show activity against *Candida albicans* and *Aspergillus flavus* fungi [45, 46, 47]. Tannins are responsible for this activity. MeOH extract of *B. disticha* shows activity against *S. aureus* and *E. coli*, with a 12 mm zone of inhibition. It also shows activity against *S. cerevisiae* fungi with an 8.0 mm zone of inhibition [48]. EtOH extract of *B. nivosa* shows activity against *B. subtilis*, *S. aureus*, and *Salmonella* Typhi. No activity is recorded against *C. albicans*, *A. fumigatus*, or *E. coli* [49].

An *in vitro* study on 96% EtOH extracts of *B. cernua* and three fractions, namely ethyl acetate, n-hexane, and water fractions, showed cytotoxicity against MCF-7 breast cancer cells with IC_{50} values of 245.841, 562.57, 165.65, and 713.78 ppm, respectively [50]. EtOH and MeOH extract (250–2500 mg/L) of *B. androgyna* possesses a cytotoxic effect on human mesenchymal stem cells, showing less cytotoxicity at higher concentrations, and more cytotoxic activity at lower concentrations [9].

Table 1. Isolated compounds of genus *Breynia*

Compound No	Compound Name	Sources	Ref.
	Alkaloids		
1	Securinine	*B. coronata* (leaf extract)	[12]
2	Allosecurinines	*B. coronata* (leaf extract)	[12]
3	Virosecurinine	*B. coronata* (leaf extract)	[12]
4	Viroallosecurinine	*B. coronata* (leaf extract)	[12]
5	Ent-Phyllanthidine	*B. coronata* (leaf extract)	[12]
	Aromatic ketones		
6	2, 4-dihydroxy-6-methoxy-3-methyl-acetophenone	*B. fruticosa* (leaf extract)	[30]
	Catechins		
7	Epicatechin	*B. retusa* (leaf, fruit, and stem bark extract)	[13]
8	Epicatechin-7-*O*-sulphate	*B. retusa* (stem bark extract)	[13]
9	Procyanidin B2	*B. retusa* (leaf and fruit extract)	[13]
	Flavonoids		
10	Kaempferol	*B. glauca* (leaf extract), *B. rtusa* (leaf and fruit extract)	[7]
11	Gallic acid	*B. retusa* (leaf and fruit extract)	[13]
12	5-Hydroxy-7, 8, 4'-trimethoxy flavone	*B. fruticosa* (leaf extract)	[14]
	Glycosides		
	i. Flavonoidal glycosides		
13	Naringenin-6,8-di-C-glucoside	*B. retusa* (leaf extract)	[13]
14	Naringenin 7-*O*- β -D-glucopyranoside	*B. fruticosa* (whole plant extract)	[15]
15	3-*O*-β-D-Glucosyl-7-*O*-α-L-rhamnosyl-kaempferol	*B. androgyna* (leaf extract)	[16]
16	3-*O*-β-D-Glucosyl-(1→6)-β-D-glucosyl-kaempferol	*B. androgyna* (leaf extract)	[16]
17	3-*O*-β-D-Glucosyl-(1→6)-β-D-glucosyl-7-*O*-α-L-rhamnosyl-kaempferol	*B. androgyna* (leaf extract)	[16]
18	Hydroquinone *O*-[6-(3-hydroxyisobutanoyl)]-β-galactopyranoside	*B. fruticosa* (leaf extract)	[17]
19	3-Acetyl-(-)-epicatechin 7-O-β-glucopyranoside	*B. fruticosa* (leaf extract)	[17]
20	3-Acetyl-(-)-epicatechin 7-O-(6-isobutanoyloxyl)- β-glucopyranoside	*B. fruticosa* (leaf extract)	[17]
21	3-Acetyl-(-)-epicatechin 7-*O*-[6-(2-methyl butanoyloxyl)]- β-glucopyranoside	*B. fruticosa* (leaf extract)	[17]
22	*(2R, 3R)*-3-Acetyl-7-methoxy-(−)-epicatechin 5-*O*-(6-isobutanoyl)-β-D-glucopyranoside	*B. fruticosa* (whole plant extract)	[18]
23	*(2R, 3R)*-3-Acetyl-7-methoxy-(−)-epicatechin 5-*O*-[6-(2-methylbutanoyl)]-β-D-glucopyranoside	*B. fruticosa* (whole plant extract)	[18]
	ii. Isoprenoid glycosides		
24	3α, 6α-Dihydroxymegastigman-7-en-9-one-3-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside	*B. fruticosa* (leaf extract)	[19]
25	Friedelan-3b-ol	*B. fruticosa* (leaf extract), *B. glauca* (leaf extract)	[7, 17]
26	Friedelin	*B. fruticosa* (leaf extract), *B. glauca* (leaf extract)	[7, 17]
27	β-Sitosterol	*B. glauca* (leaf extract)	[7]
28	3-Oxo-sitosterone	*B. glauca* (leaf extract)	[7]
29	Corchoionoside C	*B. androgyna* (leaf extract), *B. rostrata* (leaf extract)	[16, 20]
30	Sauroposide	*B. androgyna* (leaf extract)	[16]

31	Betulalbuside A	*B. officinalis* (leaf extract)	[21]
32	(5Z)-6-[5-(2-Hydroxypropan-2-yl)-2-methyl-tetrahydrofuran-2-yl]-3-methylhexa-1, 5- dien-3-O-b-glucopyranoside	*B. fruticosa* (leaf extract)	[17]
33	Isolariciresinol 3R-*O*- β -D-glucopyranoside	*B. rostrata* (leaf extract)	[22]
	iii. Ionol glycosides		
34	Alangionoside A	*B. fruticosa* (leaf extract)	[23]
35	Alangionoside B	*B. fruticosa* (leaf extract)	[24]
	iv. Megastigmane glucosides		
36	Icariside B2	*B. fruticosa* (leaf extract)	[25]
37	Boscialin 4'-*O*-β-D-glucopyranoside	*B. fruticosa* (leaf extract)	[26]
38	Byzantionoside B	*B. rostrate* (leaf extract)	[27]
39	*(3S, 5R, 6S, 9S)*-Megastigman-7-ene-3, 6, 9-triol 9-*O*-β-D-glucopyranoside	*B. officinalis* (leaf extract)	[21]
40	Breyniaionoside A	*B. officinalis* (leaf extract)	[21]
41	Breyniaionoside B	*B. officinalis* (leaf extract)	[21]
42	Breyniaionoside C	*B. officinalis* (leaf extract)	[21]
43	Breyniaionoside D	*B. officinalis* (leaf extract)	[21]
	v. N-glycosides		
44	Guanosine	*B. androgyna* (leaf extract)	[16]
45	Adenosine	*B. androgyna* (leaf extract)	[16]
46	5′-Deoxy-5′-methylsulphinyl-adenosine	*B. androgyna* (leaf extract)	[16]
47	Uridine	*B. androgyna* (leaf extract)	[16]
	vi. Phenolic glycosides		
48	*Cis-p*-coumaric acid 4-*O*-(2'-*O*-β-D apiofuranosyl)- β-D-glucopyranoside	*B. fruticosa* (leaf extract)	[28]
49	*Trans-p*-coumaric acid 4-*O*-(2'-*O*-β-D-apiofuranosyl)-β-D-glucopyranoside	*B. fruticosa* (leaf extract)	[28]
50	Robustaside A	*B. officinalis* (leaf extract)	[21]
51	Examin	*B. officinalis* (leaf extract)	[21]
52	Isorobustaside A	*B. officinalis* (leaf extract)	[21]
53	2-Phenylethyl - β D-glucopyranoside	*B. fruticosa* (leaf extract)	[29]
54	Benzyl 6-O-β-D-apiofuranosyl- β -D-glucopyranoside	*B. rostrata* (leaf extract)	[17]
55	4-(4-*O*-β-Glucopyranosyl-phenoxy)-1-*O*-β-βglucopyranosyl-1, 3-benzenediol	*B. fruticosa* (leaf extract)	[17]
56	7, 8-Erythro-dihydroxy- 3, 4, 5-trimethoxy-phenyl-propane8-*O*-β-glucopyranoside	*B. fruticosa* (leaf extract)	[17]
57	Arbutin	*B. fruticosa* (leaf extract), *B. rostrata* (leaf extract), *B. glauca* (leaf extract)	[7, 30, 31]
58	Phlebotrichin	*B. rostrata* (leaf extract)	[32]
59	*Cis-p*-coumaric acid 4-Oβ-D-glucopyranoside	*B. rostrata* (leaf extract)	[28]
60	*(3S, 6R)-Cis*-linalool-3,6-oxide β-D-glucopyranoside	*B. rostrata* (leaf extract)	[23]
61	Kaempferol-3-*O*-rutinoside	*B. glauca* (leaf extract)	[7]
62	Quercetin-3-*O*-glucoside	*B. glauca* (leaf extract), *B. rtusa* (leaf and fruit extract)	[7] [13]
63	6-*O*-Benzoylarbutin	*B. vitis-idaea* (leaf extract)	[33]
64	Breynioside B	*B. vitis-idaea* (leaf extract), *B.officinalis* (leaf extract)	[21, 33]
65	Breynioside A	*B. officinalis* (leaf extract)	[21]
66	6-*O*-Benzoyl-*α*-D-glucose	*B. vitis-idaea* (leaf extract)	[33]
67	Syringin	*B. fruticosa* (leaf extract)	[34]
68	(+)-3α-*O*-β-Glucosyl-isolariciresinol	*B. androgyna* (leaf extract)	[16]
69	(−)-3α-*O*-β-Glucosyl-isolariciresinol	*B. androgyna* (leaf extract)	[16]

70	(−)-3α-*O*-β-Apiofuranosyl-(1→2)-*O*-β-glucosyl-isolariciresinol	*B. androgyna* (leaf extract)	[16]
71	(+)-Di-*O*-β-glucosyl-syringaresinol	*B. androgyna* (leaf extract)	[16]
	vii. Simple Glycoside		
72	6-*O*-Methylpropanoyl-alpha-D-glucopyranoside	*B. rostrata* (leaf extract)	[35]
73	6, 7-Dimethylbenzofuranol 5-*O*-β-xylopyranosyl-(1→6)-β-glucopyranoside	*B. rostrata* (leaf extract)	[17]
74	(-)-5′- β -D-Glucopyranosyloxyjaamonic acid	*B. fruticosa* (leaf extract)	[36]
75	(-)-5′- β -D-Glucopyranosyloxyjaamonic acid methyl ester	*B. rostrata* (leaf extract)	[36]
	viii. Sulfur-containing spiroacetal glycoside		
76	4-[(Carboxymethyl)thio]-5′-hydroxyphyllaemblic acid *O*-β-D-glucopyranosyl-(1 →2)-β-D-glucopyranoside ester	*B. fruticosa* (whole plant extract)	[18]
	ix. Spiroketal glycosides		
77	Breinin B	*B. fruticosa* (whole plant extract), *B. retusa* (stem bark extract)	[8, 13]
78	Breinin D	*B. fruticosa* (whole plant extract), *B. retusa* (stem bark extract)	[8, 13]
79	Epibreinin B	*B. fruticosa* (whole plant extract)	[8]
80	Epibreinin D	*B. fruticosa* (whole plant extract), *B. retusa* (stem bark extract)	[8, 13]
	Lignans		
81	Aviculin	*B. fruticosa* (leaf extract)	[37]
	Neolignan		
82	2R, 3R-2,3-Dihydro-2-(40-hydroxy-30-methoxyphenyl)-3-(glucosyloxymethyl)-7- hydroxy-5-benzofuranpropanol	*B. fruticosa* (leaf extract)	[38]
83	9,9'- Hydroxy-3,4- methylenedioxy-3′-methoxy [7-O-4′ , 8–, 8-5’5′] neolignan	*B. rostrate* (leaf extract)	[39]
84	8-*O*-4'-Neolignan 3'-*O*- β -glucoside	*B. rostrate* (leaf extract)	[40]
	Steroids		
85	3β, 20β-diol-stigmast-5-ene	*B. androgyna* (leaf extract)	[16]
86	3β, 20β-diol-stigmasta-5,24(28)-diene	*B. androgyna* (leaf extract)	[16]
	Terpenoids		
87	Dihydrophaseic acid	*B. rostrata* (leaf extract)	[41]
88	Arborinone	*B. fruticosa* (leaf extract)	[14]
89	Isoarborinol	*B. fruticosa* (leaf extract)	[14]
	Tannins		
90	1-*O*-galloyl-beta-D-glucopyranoside	*B. rostrata* (leaf extract)	[35]

The EtOAc extract of *B. vitis-idaea* leaves shows antioxidant and tyrosinase inhibitory activity. To detect antioxidants, the most widely used chromogens are the stable free radical DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azino-bis(3-ethylbenzothiazoline)-6-sulphonic acid), respectively. The DPPH or ABTS assay on the EtOAc extract of leaves shows the highest activity with an IC_{50} value of 85.2 ± 0.1 µg/mL; the *n*-BuOH extract of leaves shows tyrosinase inhibition activity with an IC_{50} value of 650 ± 0.9 µg/mL. Due to the presence of phenolic compounds (hydroxyl group), they show scavenging activity [28]. Hexane, EtOAc, and MeOH extracts of *B. glauca* leaves show antioxidant activity at a concentration of more than 50 µg/mL (due to the presence of kaempferol-3-*O*-rutinoside and quercetin-3-*O*-glucoside) [7]. Different assays for xanthine oxidase (XOD) and elastase were performed on petroleum ether, MeOH, DMSO with water, or simply with DMSO extracts of *B. disticha* leaves and bark. The results indicate that the leaf and bark extract of *B. disticha* exhibits 32%, 16%, 44%, and 32% inhibition of XOD and elastase [51]. EtOH and $CHCl_3$ extracts of *B. retusa* leaves and stem show activity with an IC_{50} value of 26, 31.2, and 25.5 µg/mL in DPPH, nitric oxide, and SOD radical scavenging assays, respectively, at a concentration of 100 µg/mL (leaves have better antioxidant activity than the stem) [52]. Proteins are the major constituents of *B. androgyna* leaves. In antioxidant testing, EtOH extract of leaves shows activity in hydroxyl radical, DPPH, reducing power, alkaline DMSO, and phosphomolybdenum assays of 55.62%, 50%, 0.286 Abs, 72.51%, and 0.198 Abs, respectively, high at a concentration of 50 µg/mL (strong activity) compared to tannic acid, standard curcumin, curcumin, and vitamin E (0.54 Abs, 62.31%, 75.38%, and 0.15 Abs, respectively). These results reveal that the leaf extract of *B. androgyna* is effective against all those diseases which are mediated by free radicals [53].

In general, phenolic compounds (block virus entry or attachment to host cells), flavonoids (selectively inhibit viral RNA propagation), glycosides (reduce viral protein expression), lignin (immunomodulatory effect), etc. are effective against viral activities [54]. In this genus, antiviral activity has been studied in only one species, *B. oblongifolia*. Aqueous extract of the whole plant shows activity against duck hepatitis B virus (DHBV), with 50% inhibition at 500 µg/mL, due to the presence of these phytochemicals. The inhibitory activity is dose-dependent (inhibition increases with an increase in dose or concentration) [10].

The hexane, EtOAc, and MeOH extracts of *B. glauca* leaves show anti-inflammatory activity at concentrations of more than 50 µg/mL (due to the presence of friedelan-3β-ol, β-sitosterol, and kaempferol) because phenolic compounds are best for anti-inflammatory activity [7]. The MeOH and n-BuOH whole plant extracts of *B. fruticosa* contain sesquiterpenoids and four breynins; their names are mentioned above. This extract prevents rats from arthritis deterioration, showing 50% inhibition at a concentration of 0.2 mg/kg; this inhibition rate was compared with that of indomethacin at a dose of 2 mg/kg. The results indicate that breynins are the toxic components of *B. fruticosa*, having strong anti-inflammatory effects [8]. Aqueous extract of *B. retusa* leaves shows 87.3% and 63.77% membrane stabilization at concentrations of 1000 and 62.5 µg/mL, respectively. The results indicate anti-arthritic and membrane stabilizing activity at higher concentrations of extract [55]. EtOH extract of *B. androgyna* leaves shows 74.17% protection in a hypotonic-induced haemolysis model and 83.60% protection in a protein denaturation model at 100 µg/mL. It protects and stabilizes red blood cell membranes [53]. This extract inhibits the discharge of lysosomal content from polyphenolic neutrophils (due to the presence of flavonoids) [9]. EtOH and MeOH extracts of *B. nivosa* leaves show 18% and 22% inhibition at 100 and 200 mg/mL (approximately equal to the percentage inhibition of diclofenac). This is done by inhibiting histamine or serotonin [49].

Ethyl acetate and MeOH extracts of *B. retusa* leaves show 98% inhibition of α-amylase at 60 µg/mL [56]. Supplementation with 90 mg/kg aqueous leaf extract of *B. androgyna* reduces LDL, VLDL, HDL, and cholesterol (due to the presence of alkaloids). Digestion of 5 g/100 mL of leaf extract significantly lowers the blood glucose level (referred to as diabetic greens) [57]. Aqueous and EtOH extracts of *B. vitis-idaea* leaves elicit a 60.89% and 63.37% decline in glucose level at 300 µg/mL of both extracts, respectively, having significant hypoglycaemic ($p < 0.001$) and hypolipidaemic ($p < 0.01$) activity [58]. Aqueous MeOH extract of *B. officinalis* whole plant shows hypocholesterolaemic activity at 0.02, 0.005, 0.01, and 0.025 mg/kg/day (due to the presence of breynin A and B). The breynin B activity is about one-fifth of the activity of breynin A [59].

EtOH extract of *B. fruticosa* whole plant shows tyrosinase inhibition with IC_{50} values of 0.89 and 0.82 respectively (due to the presence of spiroacetal glycosides, i.e. compounds **19**, **21**, **22**, and **23**). Tyrosinase is a copper-containing enzyme that catalyses the production of melanin. Tyrosinase inhibitors specifically inhibit melanogenesis in the cell without side effects [13].

Gold and silver nanoparticles synthesized from the stem bark of *B. rhamnoides* show an efficient reduction of 4-nitrophenol to 4-aminophenol [60]. In the body, accumulation of 4-nitrophenol causes blood disorders, such as reducing the oxygen-carrying capacity of the blood [61].

Table 2. Biological activity of species of the genus *Breynia*

Pharmacological activity	Plant sources	Results	Reference
Antimicrobial activity	*B. retusa*	EtOH extract of leaves is more effective against *Salmonella* Typhimurium, *E. coli*, and *Enterobacter aerogenes* and less effective against *Micrococcus luteus*	[43]
	B. cernua	EtOH extract of leaves is more effective against *Trichophyton rubrum*, *Aspergillus niger*, and *Penicillium* sp. and less effective against *Cryptococcus* sp. fungi Petrol, CH_2Cl_2, BuOH, EtOAc, and MeOH extracts of leaves are effective against all fungi	[44]
	B. androgyna	MeOH and EtOH extracts of leaves are effective against *Proteus vulgaris*, *Bacillus cereus*, *Staphylococcus aureus*, *E. coli*, *Klebsiella pneumonia*, Gram-positive bacteria (MeOH extract shows more inhibition than EtOH extract) EtOH extract of leaves is effective against *Candida albicans* and *Aspergillus flavus*	[45, 46] [47]
	B. disticha	MeOH extract is effective against *S. aureus* and *E. coli* and effective against *S. cerevisiae* fungus	[48]
	B. nivosa	EtOH extract of leaves is effective against *B. subtilis*, *S. aureus*, and *Salmonella* Typhi	[49]
Cytotoxic activity	*B. cernua*	n-Hexane fraction shows good cytotoxic activity against MCF-7 breast cancer cells (IC_{50} 165.65 ppm)	[50]
	B. androgyna	EtOH and MeOH leaf extract (250–2500 mg/L) shows a cytotoxic effect on human mesenchymal stem cells	[9]
Antioxidant activity	*Breynia vitis-idaea*	DPPH or ABTS assay of EtOAc extract of leaves shows highest activity (IC_{50} 85.2 ± 0.1 µg/mL) and *n*-BuOH extract of leaves shows tyrosinase inhibition activity (IC_{50} 650 ± 0.9 µg/mL)	[28]
	B. glauca	Hexane, EtOAc and MeOH extracts of leaves show activity at concentrations greater than 50 µg/mL (due to the presence of kaempferol-3-*O*-rutinoside)	[7]
	B. disticha	Petroleum ether, MeOH, and DMSO extracts of leaves and bark inhibit XOD and elastase by 32%, 16%, 44%, and 32%, respectively	[51]
	B. retusa	EtOH and $CHCl_3$ extracts of leaves and stem show activity with IC_{50} of 26, 31.2, and 25.5 µg/mL in DPPH, nitric oxide, and SOD radical scavenging assays at 100 µg/mL	[52]
	B. androgyna	EtOH extract of leaves shows activity in hydroxyl radical, DPPH, reducing power, alkaline DMSO, and phosphomolybdenum assays of 55.62%, 50%, 0.286 Abs, 72.51%, 0.198 Abs, respectively, high at 50 µg/mL	[53]
Antiviral activity	*B. oblongifolia*	500 µg/mL aqueous extract of whole plant shows 50% inhibition against duck hepatitis B virus (DHBV)	[10]

Anti-inflammatory activity	*B. glauca*	Hexane, EtOAc, and MeOH extracts of leaves show activity at concentrations greater than 50 µg/mL (due to the presence of friedelan-3β-ol, β-sitosterol, and kaempferol)	[7]
	B. fruticosa	MeOH and n-BuOH whole plant extracts prevent rats from arthritis deterioration with 50% inhibition at 0.2 mg/kg (due to the presence of sesquiterpenoids and breynins)	[8]
	B. retusa	Aqueous extract of leaves shows 87.3% and 63.77% membrane stabilization at 1000 and 62.5 µg/mL and moderate anti-arthritic activity	[55]
	B. androgyna	EtOH extract of leaves shows 74.17% and 86.88% protection and stabilization to membranes of red blood cells at 100 µg/mL	[53] [9]
	B. nivosa	EtOH and MeOH leaf extracts show 18% and 22% inhibition at 100 and 200 mg/mL	[49]
Antidiabetic activity	*B. retusa*	EtOAc and MeOH extracts of leaves show 98% inhibition of α-amylase at 60 µg/mL	[56]
	B. androgyna	Supplementation with 90 mg/kg aqueous extract of leaves reduces LDL, VLDL, HDL, and cholesterol; digestion of leaves lowers the blood glucose level	[57]
	B. vitis-idaea	Aqueous and EtOH extracts of leaves show a 60.89% and 63.37% decline in glucose level at 300 µg/mL of both extracts, respectively, having significant hypoglycaemic ($p < 0.001$) and hypolipidemic ($p < 0.01$) activity	[59]
	B. officinalis	Aqueous MeOH extract of whole plant shows hypocholesterolaemic activity at 0.02, 0.005, 0.01, and 0.025 mg/kg/day	[59]
Enzyme inhibition	*B. fruticosa*	EtOH extract of the whole plant shows tyrosinase inhibition with IC_{50} values of 0.89 and 0.82, respectively	[13]
Blood disorder	*B. rhamnoides*	Gold and silver nanoparticles of this species reduced 4-nitrophenol to 4-aminophenol (accumulation of 4-nitrophenol causes blood disorder)	[61]

4. Conclusion

The species of this genus are widely distributed in Australia, Malaysia, Vietnam, and India. A total of 90 compounds are mentioned in this review; these secondary metabolites are very effective for the treatment of several diseases, like cancer, arthritis, diabetes, fever, cough, and blood disorders, and act as antioxidants. This antioxidant activity can be proved best for the treatment of many diseases, which are caused due to oxidative stress, like for the treatment of neurodegenerative disorders. There are about 38 species in this genus, out of which the pharmacology and phytochemistry of ten species have been identified. In this way, much more consideration ought to be paid to sort *Breynia* for the disclosure of novel phytochemicals and their pharmacological assessment. This will help to cope with various diseases by introducing novel therapeutic agents to the world health community.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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