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Systematic Review

The Genus *Bryonia* L. (Cucurbitaceae): A Systematic Review of Its Botany, Phytochemistry, Traditional Uses, and Biological Activities

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Abstract: The *Bryonia* genus (Cucurbitaceae) is divided into 13 plants considered medicinal species with a significant pharmacological value fortreating as well as preventing various ailments. The current systematic review aims to present useful and updated findings published onthis genus inthe last two decades. Based on PubMed, Science Direct, JSTOR, and Google Scholar, 42 of the available previous studies on *Bryonia* have been selected from 2000 to 2022. Thereafter, these studies were analyzed, summarized, and separately recorded according to the topic or section, adding some comments foreach. Our review provided a botanical description of the genus, followed by itsindigenous uses. Furthermore, more than 150 reported phytochemical compounds were grouped into families such as terpenoids, alkaloids, flavonoids, glycosides, saponins, and volatile oils. Hereby, thebiological activities part of this genus wereexposed, including itsantimicrobial, antioxidant, antidiabetic, antinociceptive, and anti-inflammatory functions, along with an interesting anticancer efficiency. Overall, our findings could contribute to forthcoming investigations that may lead to determining the responsible phytoconstituents for *Bryonia*'s efficiency.

Keywords: *Bryonia*; systematic review; phytochemistry; botany; biological activities

Citation: Benarba, B.; Belhouala, K. The Genus *Bryonia* L. (Cucurbitaceae): A Systematic Review of Its Botany, Phytochemistry, Traditional Uses, and Biological Activities. *Sci* **2024**, *6*, 7. https://doi.org/10.3390/sci6010007

Academic Editor: Fernando Lidon

Received: 13 December 2023
Revised: 29 December 2023
Accepted: 15 January 2024
Published: 18 January 2024

1. Introduction

Sinceantiquity, the world population has resorted to plants for medical purposes in order to provide for their healthcare needs [1]. Today, about 80% of itrelies on folk phytotherapy involving indigenous knowledge, traditional culture, and medicinal herbs from itssurroundings [2]. Certain plant families offer a highly curative effect with a worldwide distribution and large diversity, such as Cucurbitaceae. This family covers almost 100 genera spread across tropical and subtropical areas [3–5]. Among these genera that have shown significant importance as medicinal plants is the *Bryonia* genus. It comprises 10 direct children (*B. cretica* L., *B. multiflora* Boiss. and Heldr., *B. monoica* Aitch. and Hemsl., *B. aspera* Steven ex Ledeb. and *B. alba* L., *B. lappifolia* Vassilcz., *B. melanocarpa* Nabiev, *B. syriaca* Boiss., *B. verrucosa* Aiton, and *B. flexuosa* Yıld.) and 3 accepted subspecies (*B. dioica* Jacq., *B. marmorata* (E. Petit) Jauzein, and *B. acuta* Desf) across dioecious and monoecious types [6,7]. Some species are widely distributed with slight morphological dissimilarities from one to another, especially in the fruits, while others have a limited range. Additionally, all *Bryonia* species have an Irano-Turanian origin, prospering in many Mediterranean regions [8]. *Bryonia* was well known in ancient times for it shealing value. In fact, various diseases were traditionally treated using *Bryonia* species, for example, infectious diseases, tissue inflammation, cough, influenza, lung disease, cancers, hemorrhoids, diabetes, peritonitis, jaundice, typhoid, bone pain, and nervous and cardiac disorders [9–12]. These diversified therapeutic uses and medicinal properties of the genus are due to interesting phytochemical components such as polyphenols, flavonoids, triterpene, glycosides, sterols, saponins, and alkaloids [13,14].

Nonetheless, a few *Bryonia* species have a significant toxic potentiality, where the most poisonous part is the roots [15,16]. Furthermore, in this smallest genus of the Cucurbitaceae family, *B. alba* Linn.and *B. dioica* Jacq. are the common species used in folk medicine as valuable remedies against serious ailments [11,17]. Despite this phytochemical and historical medical distinction of *Bryonia*, the species from this genus still face scientific deficiency, with slight interest shown in recent studies. Therefore, the present study aimed to systemically summarize the botanical, ethnobotanical, biological, and phytochemical properties of species belonging to the genus *Bryonia*. Moreover, this systematic review ended the controversy over the exact number of *Bryonia* species.

2. Methodology

In accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), the current systematic review was designed and reported.

2.1. Search Strategy

The search was conducted inthe following databases: the JSTOR "www.search.scielo.org (accessed on 30 December 2022)", PubMed® "www.pubmed.ncbi.nlm.nih.gov (accessed on 30 December 2022)", ScienceDirect® "www.sciencedirect.com/search (accessed on 30 December 2022)", and Google Scholar "www.scholar.google.com (accessed on 30 December 2022)" databases. The term "*Bryonia*" was the main word used in the searches individually or in association with other keywords such as "botany", "phytochemistry", "GC-MS", "HPLC", "pharmacology", "biological activity", "ethnomedicine", "traditional use", "cancer", "anticancer", "antiproliferative", "antitumor", "cytotoxicity", and "toxicity". The accepted species of this genus were obtained from thedatabases The Plant List (TPL) (www.theplantlist.org/, accessed on 30 December 2022), World Flora Online (WFO) (www.worldfloraonline.org/, accessed on 30 December 2022), and Plants of the World Online (POWO) (www.powo.science.kew.org/, accessed on 30 December 2022), validating their scientific names. Moreover, we adopted the Boolean operator "AND" in the searches that contained two or more of these keywords.

2.2. Study Selection

With the use of only verified accepted species names and selected keywords in the search and analysis, articles published in the last 22 years (2000–2022) reporting specifically botanical, phytochemical, pharmacological, and toxicological data on *Bryonia* species were included, following the following eligibility criteria:

(1) Validated source of material: plant materials were identified to the taxonomic levels of genus and species.
(2) Appropriate methodology: standard methods for pharmacological assays both in vitro and in vivo were employed, along with phytochemical investigation.
(3) Access to the full-text article in the English language: articles published only in non-English languages were excluded.

On the other hand, review articles, e-books, book chapters, and doctoral theses were excluded. Moreover, articles with titles containing the word *Bryonia* as synonyms of other species not referring to the genus *Bryonia* or even unverified names, not dealing with the previous search terms, and not available in the full text were excluded.

2.3. Data Extraction

Overall, 111 scientific documents were selected from the databases and screened. After reading the title and/or abstract, 26 documents that did not fit into the scope of this review were excluded. A total of 44 articles had their full text analyzed, being screened by the title, abstract, and specific information throughout the text. Consequently, 42 articles with data on the traditional uses, pharmaceutical activities, phytochemicals, and toxicity of *Bryonia* species were included in this study. The available information on *Bryonia*

was categorized into many sections: botanical description, phytochemicals and bioactive-compounds, traditional uses of *Bryonia*, in vivo and in vitro pharmacological studies, and the anticancer and toxicity potential of *Bryonia*. The identification and selection process isillustrated in Figure 1.

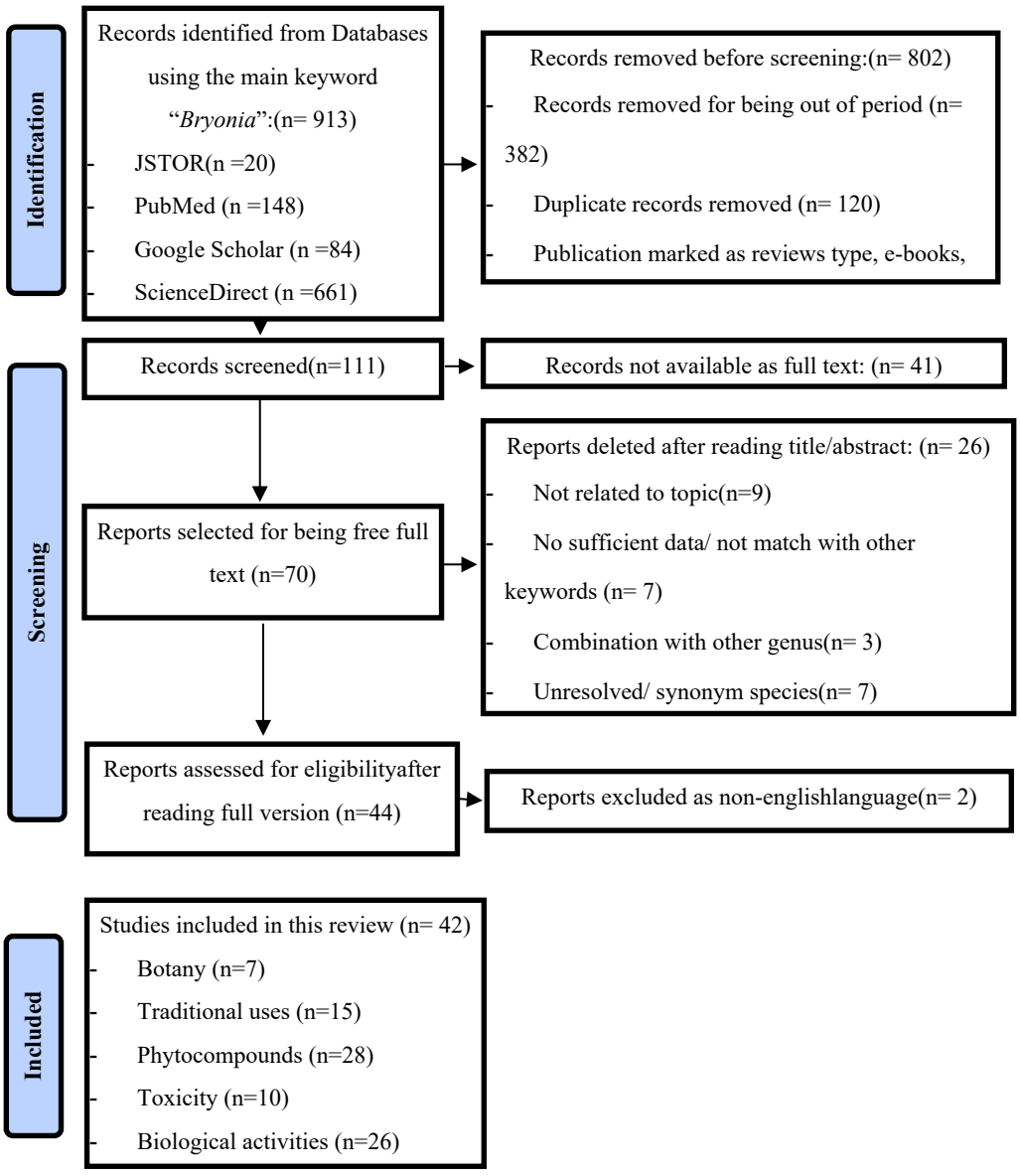


Figure 1. Identification and selection process of the bibliographic sources based on a PRISMA 2020 flow diagram.

3. Results and Discussion

3.1. Botany (Taxonomy, Description, and Distribution)

The *Bryonia* genus belongs to the Cucurbitaceae family and comprises 13 known taxa with accepted names (Table 1). Previously, *B. alba*, *B. verrucosa*, *B. syriaca*, *B. lappifolia*, *B. cretica*, *B. multiflora*, *B. monoica*, *B. melanocarpa*, and *B. aspera* were the only accepted species included in the *Bryonia* genus, while the status of the 10th species (*B. flexuosa* Yıld) was reported as unresolved [18]. According to the recent articles and updated taxonomy (POWO and WFO), the genus *Bryonia* includes a total of 10 accepted direct species and 3 subspecies, namely *B. acuta*, *B. marmorata*, and *B. dioica*, considered *B. cretica* subspecies [6,7,19–21]. In the same line, Tutin et al. (2010) reported the presence of three subspecies belonging to the *B. cretica* species [4].

Table 1. *Bryonia* accepted species and subspecies according to WFO and POWO databases [6,7].

Scientific Name	Status	Synonym
Bryonia alba L.	Accepted	*B. dioica* M.Bieb. *B. monoeca* E.H.L.Krause *B. nigra* Gilib. *B.vulgaris* Gueldenst ex Ledeb.
Bryonia aspera Steven ex Ledeb.	Accepted	*B. afghanica* Podlech *B. haussknechtiana* Bornm. *B. macrostylis* Heilbr. and Bilge
Bryonia cretica L.	Accepted	*B. cretica* f. *monoica* (Nábělek) Feinbrun *B. cretica* var. *Monoica* Nábělek
Bryonia cretica subsp. *acuta* (Desf.) Tutin	Accepted	*B. acuta* Desf. *B. dioica* var. *acuta* (Desf.) Cogn.
Bryonia cretica subsp. *dioica* (Jacq.) Tutin	Accepted	*B. dioica* Jacq. *B. ruderalis* Salisb. *B. scarlatina* Dumort. *B. acuta* var. *sicula* (Jan) Fiori and Paol. *B. digyna* Pomel *B.dioica* var. *digyna* (Pomel) Batt. *B. dioica* var. *elongata* Ten. *B.dioica* var. *lavifrons* Pau *B.dioica* var. *lutea* Ser. *B. dioica* var. *sicula* Jan *B.lutea* Bastard ex Ser. *B.nitida* Link *B.sicula* (Jan) Guss. *B.tineoi* A.Huet ex Cogn
Bryonia cretica subsp. *marmorata* (E.M.A.Petit) Jauzein	Accepted	*B. angulosa* (Mabille ex Gillet) Bouchard *B. corsica* (Maire) A.W. Hill *B. cretica* subsp. *marmorata* (E. Petit) Govaerts *B. dioica* f. corsica Maire *B. dioica* var. *angulosa* Mabille ex Gill. *B. marmorata* E.Petit *B. syriaca* var. *marmorata* (Petit) Fiori and Paol
Bryonia lappifolia Vassilcz.	Accepted	
Bryonia melanocarpa Nabiev	Accepted	
Bryonia monoica Aitch. and Hemsl.	Accepted	*B. transoxana* Vassilcz
Bryonia multiflora Boiss. and Heldr.	Accepted	*B. lasiocarpa* Mouterde *B. macrophylla* Kotschy ex Boiss. *B. macrophylla* var. *condensata* Boiss. *B. subsessilis* (Boiss.) Bornm
Bryonia syriaca Boiss.	Accepted	*B. micrantha* Boiss. *B. multiflora* var. *pauciflora* Post *B. syriaca f. monoica* Feinbrun
Bryonia verrucosa Aiton	Accepted	*B. hederifolia* Jacq.
Bryonia flexuosa Yıld.	Accepted	

Bryonia species are flowering annual herbs defined by tuberous roots, palmate-lobed leaves (about 3–5 at sharp angles), small flowers with threestamens, and several types of spherical berries with oblate–ovoid seeds. On the contrary, these bryonies show non-similar external morphological characteristics differing from one species to another.

As shown in Table 2, almost all *Bryonia* species flower in spring (March to May), while the flowering of other species may extend into summer (*B. alba* and *B. cretica*). The flowers are green or yellow or even a mixed color between the two, together forming a tiny greenish yellow mass of 3–4 flowers on the stem, which climbs in threes due to itslong tendrils. On the other hand, *B. dioica* has blue or white flowers [11]. With the exception

of *B. alba*, *B. monoica*, and *B. aspera*., all *Bryonia* species are dioecious, and their ripe fruits are often red, having a similar shape. Moreover, the macroscopy details are still poorly described for *B. melanocarpa*, *B. marmorata*, and *B. lappifolia* besides the anatomical structures of all species.

Table 2. Description and distribution of *Bryonia* species.

Species	Vernacular Names	Native to	Flowering	Macroscopy Details			Reproduction	Ref.
				Fruit	Leaves	Flower		
B. dioica Jacq.	Red bryony Fashra	Central/Southern Europe, North Africa, Western Asia	May	red	five-pointed	blue or white	dioecious	[11]
B. alba L.	White bryony	Central, E. and S.E. Europe to Kazakhstan	May–June/July	black fruits	5-angular, irregular palmate	whitish, green-veined	monoecious	[19,22]
B. acuta (Desf.) Tutin		Algeria, Libya, Sicilia, Tunisia		bright red	3–5 lobed	white	dioecious	[8]
B. marmorata E. Petit		Corse, Sardegna					dioecious	[8]
B. verrucosa Aiton		Canary Islands	March to May	orange–yellow	rough and warty	greenish-white to light yellow	dioecious	[8]
B. syriaca Boiss.		Lebanon–Syria, Palestine, Sinai		red	Palmate, three-pointed		dioecious	[8]
B. lappifolia Vassilcz.		Tadzhikistan						
B. cretica L.		Europe to N. Africa and Central Asia	May to August	bay	palmate	green	dioecious	[8,22]
B. multiflora Boiss. and Heldr.		Turkey, S. Syria, N. Iraq, W. and S.W. Iran	March–April	purple berries	palmate and have 5–7 deep lobes	yellow	dioecious	[8]
B. monoica Aitch. and Hemsl.		N.E. Iran to Central Asia and Pakistan			orbicular	yellowish green	monoecious	[8]
B. melanocarpa Nabiev		Kazakhstan, Uzbekistan		black				[23]
B. aspera Steven ex Ledeb.	Rough Bryony (Andaz)	Pakistan, N.W. India, N. Afghanistan, N. and N.E. Iran, Caucasus, and Turkey		red or yellow	heart-shaped-cordate–ovate, five-lobed	corymbose, yellow	monoecious	[24]
B. flexuosa Yıld.		Turkey, the Mediterranean			alternate	White/yellow, tubular		

Owing to their adaptability, *Bryonia* species are widely dispersed all over the world and cultivated in different environmental conditions, which may explain their distribution in different regions such as the Mediterranean to Central European territories, Northern Africa, and Central Asia [25]. Nonetheless, some species are considered native to specific regions such as *B. dioica* and *B. cretica* from North Africa (Algeria, Morocco) and Western Europe and *B. multiflora*, *B. aspera*, and *B. alba* from Turkey [3,26,27].

3.2. Traditional Uses

Bryonia species have been used for centuries to treat different diseases or manage a variety of disorders with a focus on theirtuberous roots' proprieties (bitter, toxic…) [8,25]. Figure 2 illustrates different disease categories treated traditionally using *Bryonia* species. Ethnobotanical studies showed that *B. dioica*, *B. aspera*, *B. alba*, and *B. cretica* are the most involved species. Nonetheless, *B. dioica* seems to be more known than others species in Northern Africa due to its anticancer property (Algeria, Morocco, and Tunisia) [2,11,28]. *B. dioica* is used to treat breast cancer, nose cancer, skin cancer, and uterus tumors as well asbruises, rheumatic pains, arthritis, minor wounds, and lesions. Other investigations reported that theroots of *B. dioica* are used as remedies for liver failure, stomachache, ulcers, and diabetes [11,15]. Furthermore, the species is used in Iraq to treat bronchitis, while the leaves and seeds are used to cure fevers using internal or external administration [29].

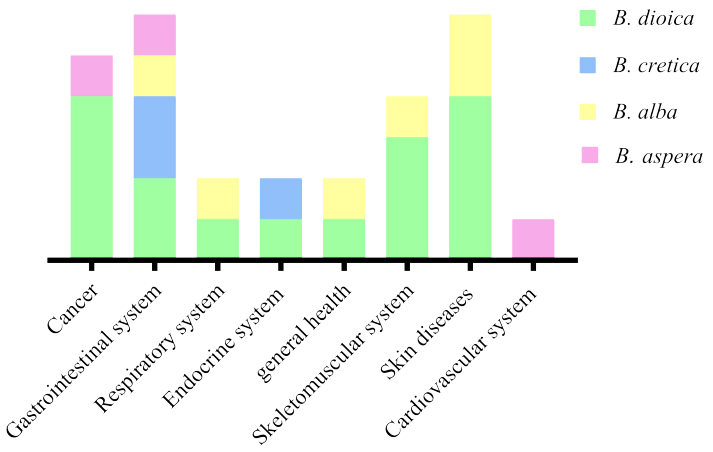


Figure 2. *Bryonia* species traditionally used to treat several ailments.

In eastern and northern Europe, the *B. alba* root has been used in diverse systems including the gastrointestinal, respiratory, and skeletomuscular systems to treat intestinal worms, convulsions, peritonitis, jaundice, headaches, and pneumonia [13]. The root extract is applied torheumatic and joint pain in Turkish folk medicine, whereas white bryony is commonly applied for the treatment of skin diseases, edemas, and bruises [21]. On the other hand, *B. aspera* was reported to be commonly used in the Turkmen Sahara region (northeast of Iran) to treat gastrointestinal and cardiac diseases and some cancer types [24,30]. Likewise, the roots of *B. cretica* were used by Egyptian healers to treat gastric disorders and diabetes [31].

3.3. Pharmacological Proprieties (In Vivo/In Vitro Application)

Different *Bryonia* species have shown interesting biological properties including antioxidant, anti-inflammatory, antibacterial, anti-parasitic, anticancer, etc. (Table 3).

- Antioxidant

Gholivand and Piryaei (2012) investigated the antioxidant ability of the methanolic extract of *B. dioica* (leaves, stems, and flowers) using DPPH scavenging, β-carotene bleaching, and reducing power tests. The polar subfraction of the flowers provided the highest radicalscavenging activity with the lowest IC_{50} value of 23.17 ± 4.24 µg/mL. Despite this result, both the polar and nonpolar subfractions of all parts provide a high radical scavenging inhibition. In the β-carotene bleaching assay, the flowers' polar subfraction and leaves' nonpolar subfraction had a notable result against linoleic acid oxidation, with inhibition values of 98.35 ± 8.7 and 83.62 ± 5.91%, respectively [32]. Likewise, a promising antioxidant potential has been demonstrated for the methanolic extract of leaves of the Iraqi *B. dioica* [33]. In another study on immature and ripened fruits of Portuguese *B. dioica*, it has been found that immature fruit extract exhibited the lowest antioxidant activity with an EC_{50} value ranging from 1.07 to 18.01 mg/mL due to its lower phenolic and flavonoid contents (33.37 and10.32 mg CE/g extract, respectively). On the other hand, the fruit extract showed an important antioxidant potential at the maturity stage (EC_{50}: 0.22–1.21 mg/mL) [34].

InRomania, more studies have focused on the antioxidation potential of *B. alba* species using different approaches (cell-free systems and cellular assays) to evaluate the peroxidase-inhibiting effect, as well as justify the antioxidant/antiradical activity of the leaf extract and its isolated flavonoids. An important inhibition of myeloperoxidase and horseradish peroxidase has been reported and shown according to its active molecules lutonarin and saponarin (IC_{50} = 0.92 ± 0.55 µg/mL). Moreover, the best inhibition of the ROS produced by neutrophils and macrophages was obtained using the isolated compounds isoorientin and lutonarin [35]. Similarly, Lelciu et al. (2019) investigatedthe antioxidant capacity of methanolic extract of *B. alba*'s aerial parts using six in vitro assays. A significant antioxidant capacity

related to the flavonoid content has been demonstrated (DPPH: IC_{50} = 99.8 ± 0.92 µg/mL; TEAC: IC_{50} = 19.9 ± 0.89 µg/mL; CUPRAC: IC50 = 238 ± 2.24; FRAP: IC_{50} = 217 ± 2.45; SNPAC: IC_{50} = 217 ± 2.45; and EPR: IC_{50} = 427 ± 2.46 µg/mL) [14]. Similar results have been reported for *B. alba* from Turkey [13].

- Anti-inflammatory

Based on the ethnomedicinal uses of some *Bryonia* species to treat inflammatory disorders, several in vitro and in vivo investigations have been carried out to evaluate the anti-inflammatory potential of *Bryonia* species, especially *B. alba* and *B. dioica* (Table 3).

Ukiya et al. (2002) evaluated the anti-inflammatory activity of MeOH extract of the *B. dioica* roots and its fractions (n-hexane, EtOAc, n-butanol, and H_2O) using an in vivo TPA-induced inflammation assessment in mice. Among the four fractions, a remarkable inhibition effect of the EtOAc-soluble fraction (inhibitory ratio 90% at 1 mg/ear) was pointed out. Moreover, the same test was further used to assess the inhibitory effects of six pure triterpene glycosides (four new compounds, bryoniosides **2**–**5**, with two known compounds, cabenoside D and bryoamaride) isolated from the EtOAc-soluble fraction. A strong anti-inflammatory effect was shown (ID_{50} = 0.2–0.7 mg/ear) against TPA-induced inflammation comparedto that of a reference drug (1.6 mg/ear) [36]. In the same line asthese findings, n-hexane, EtOAc, and MeOH extracts of *B. alba* exhibited promising in vivo anti-inflammatory effects [13]. Likewise, an extract of *B. alba* leaves and its flavonoids showed anti-inflammatory effects through the inhibition of the pro-oxidant enzyme myeloperoxidase [17].

- Antibacterial

As shown in Table 3, the antibacterial activity of *B. dioica* was tested on nine bacterial strains. Significant antimicrobial activity has been reported against three of them: *E. coli*, *K. pneumonieae*, and *P. valgaris* [33]. Furthermore, Dhouioui et al. (2016) stated that Gram-positive bacteria were more susceptible to the lipid fraction of *B. dioica* roots than that of the fruits. However, the lipid fractions extracted from both plant parts were less active than antibiotics [37].

- Antiparasitic

By using two parasitic strains 3D7 (chloroquine sensitive) and W2 (chloroquine resistant), an extract *B. alba*'s aerial partswas tested for its anti-plasmodialpotential, showing no cellular toxicity inthese Plasmodium falciparum strains [14].

- Anti-infection

In a study carried out by Goswami et al. (2022), a 14-day-old chick embryo (*Gallus gallus domesticus*) inoculated with recombinant Delta SARS-CoV-2 spike RBD protein was injected with a diluted ethanolic extract of *B. alba* before the inoculation as pretreatment and after the inoculation as post-treatment. The results showed that the *B. alba* extract was able to upregulate IFN-α and IL-10, especially in post-treatment, indicating an immunomodulatory effect through a pro-inflammatory cytokine decrease [38].

- Antidiabetic

Chekroun et al. (2017) used astreptozotocin (STZ)-induced diabetic rat model to establish the antidiabetic effect of *B. dioica* root aqueous extract. After 21 days of daily treatment using the *B. dioica* extract (20 mg/kg i.p), the *B. dioica* extract exhibited a similar effect to the standard drug inreducingtheblood glucose levels by −59% and −51%, respectively, restoring the normal biochemical parameters levels, as well as reversing the reduction in body weight of the rats [39]. Likewise, Uyar et al. (2017) investigated the protective effects of *B. multiflora* extract on pancreatic, liver, and kidney cells. The findings showed a significant increase in the insulin antibody immune-positive areas for thetreated groups with extract doses of 100, 200, and 400 mg/kg BW/day, inducing a significant improvement in the beta cells' function. Besides this effect, *B. multiflora* extract was found to inhibit the damage

formed in the liver, kidneys, and pancreas; hence, the ability of the plant inthe treatment of diabetes and its complications has been connected to its antioxidant activity [40].

- Hepatoprotective effect

Kadhim (2014) investigated the hepatoprotective action of anethanolic extract of *B. dioica* leaves on rats with CCl4-induced hepatotoxicity. This assay was based on examination of the transaminase (ALT and AST) activity and the histopathological changes in the rats' livers. The results confirmed the protective capacity of *B. dioica* against the toxic effects of CCL4 since the extract showed the recovery of the hepatic architecture from CCL4-induced necrosis and of the decline in the ALT and AST activities to a normal level [29].

- Antinociceptive

The antinociceptive ability of ethyl acetate extract obtained from *B. alba* roots was assessed using p-benzoquinone-induced abdominal constriction and tail flick tests in mice. The first assay showed a significant antinociceptive effect with the lowest writhing number of 26.0 $\pm$ 4.3 compared to those of the other extracts (n-hexane and methanolic) and identical to that of the reference drug (aspirin). However, none of the extracts prepared from *B. alba* roots showed any activity in the second assay [13].

- Anti-polycystic ovary syndrome

In a recent experiment by Tahvilian et al. (2022), a *B. dioica* root methanolic extract was evaluated against polycystic ovary syndrome in female rats receiving subcutaneous injections of testosterone enanthate. After 28-day treatment, the hormone (FSH and LH) and glucose levels were significantly normalized besides a decrease in theLDL level and LDL/HDL ratio in the *B. dioica* groups, showing an ameliorative as well as a preventive effect on PCOS-induced rats [41].

- Anticancer

Increasing evidence emphasizes the anticancer activity of *Bryonia* species, especially that of its cucurbitacin constituents, given an interesting anticancer profile to this genus. These triterpene-type compounds, mainly obtained from the root parts, present potential as biomarkers in herbal therapy, showing particular promise as anticancer agents, with a general mechanism based on cell cycle blockage and programmed death, like apoptosis or autophagy [42]. Cucurbitacins exert their cytotoxic effects against cancer cells by inhibiting their proliferation, invasion, and migration [43].

Anethanolic extract of *B. cretica* roots was found to exhibit important antiproliferative action againsthuman leukemia U937 cells. Furthermore, two cucurbitane-type triterpenes (cucurbitacins B and E) isolated from the same extract displayed a comparable effect oncell growth inhibition with IC_{50} values of 9.2 and 16 nM after 72 h, respectively, along with that of camptothecin (8.6 nM) [31]. Likewise, cucurbitacin E showed a strong cytotoxic activity (IC_{50} = 40 nM after 72 h) on HT1080 cells dissimilar to that of isocucurbitacin D (0.71 uM) [44]. Moreover, Pourgonabadi et al. (2017) reported thesignificant inhibitory activity and apoptotic effects exerted by a hydro-alcoholic root extract of *B. aspera* against Hela and HN-5 cell lines [30]. In another study, *B. aspera* methanolic extract induced thecell death and apoptosis of B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL) [45]. Similar results were reported for achloroform extract of *B. aspera* roots and two of its identified compounds (cucurbitacin L, and neocucurbitacin C) [46]. Significant cytotoxic activity has been exerted by *B. aspera* species against different tumor cells, including MCF7 (human breast adenocarcinoma), HepG2 (hepatocellular carcinoma), and WEHI (mouse fibrosarcoma) [45].

B. dioica has also been studied for its anticancer effects. Indeed, several studies have demonstrated that different extracts of the species were able to inhibit the growth of cancer cells, induce apoptosis, and result in cell cycle arrest through a variety of molecular mechanisms. Benarba et al. (2012) demonstrated that anaqueous extract of *B. dioica* roots

significantly inhibited the cell growth of the Burkitt's lymphoma BL41 cell line by inducing apoptosis through the mitochondrial pathway (activation of caspase-3 and caspase-9, PARP cleavage, and loss of the mitochondrial membrane potential) [28]. In another study, Benarba et al. (2019) found that the same extract at a lower concentration (50 µg/mL) was able to induce both apoptosis and G2/M cell cycle arrest in MDA-MB 231 breast cancer cells. This anticancer activity was attributed to its identified major phenolic compound myricetin [47]. Furthermore, amethanol extract of *B. dioica* showed in vitro and in vivo anticancer effects against B16F10 melanoma cells, in which the cucurbitacins obtained from this extract were able to induce apoptosis, as well as arrest cell cycle progression [48].

Other studies based on anti-inflammatory analysis have demonstrated that the triterpenes from *B. dioica* roots areexpected to have a high anti-tumor-promoting role inmice. Likely, a compound isolated from *B. dioica*, namely bryoside, has been noticed as an anti-inflammatory and anti-tumor agent [36].

3.4. Phytochemistry and Bioactive Compounds

Phytochemical studies on *Bryonia* species have led to the isolation and identification of approximately 150 primary and secondary metabolites to date (Figure 3). Table 4 shows their names, types, corresponding plant sources, and the nature of the extracts, with an illustration of some of the main compound structures in Figures 4–8.

As primary metabolites, elements have the highest percentage with 19 compounds, followed by fatty acids with 15 compounds, and sugars with 12 compounds (Figure 3). In fact, at the time of writing this review, the presence ofboth sugars (8%) and vitamins (5%) has been reported in only two species of *Bryonia*: *B. dioica* and *B. alba*. Meanwhile, elements (12%) were particularly detected in *B. dioica*. Likewise, a few proteins (four compounds) such as lectin, bryodiofin, and bryodin were found in the *B. dioica* roots.

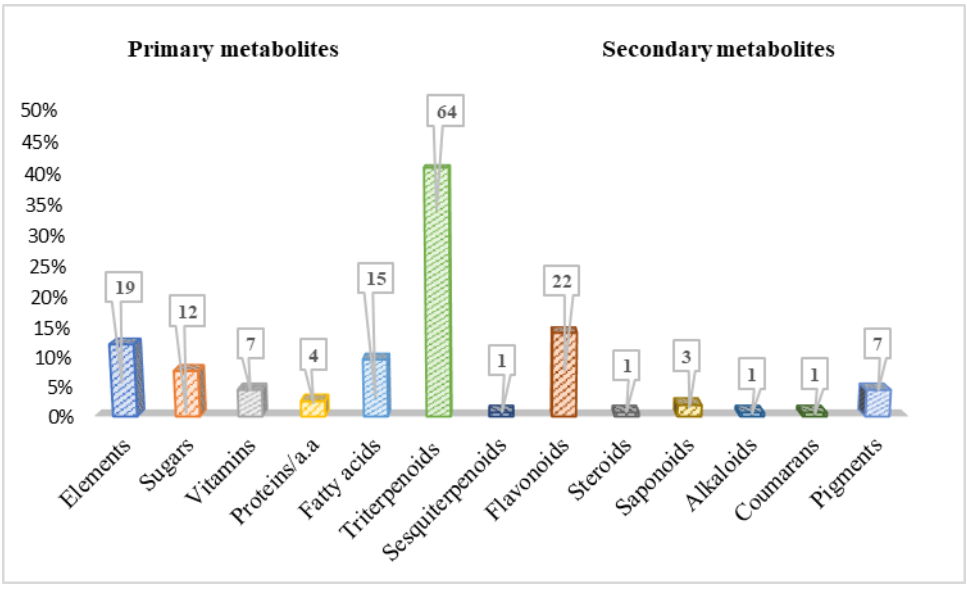


Figure 3. Phytoconstituent classes found in *Bryonia* species.

Considering secondary metabolites, this review reports a total of 100 compounds identified in this genus from 2000 to the present day (Table 4). Predominantly, the terpenoidclass was detected in *Bryonia* species, including triterpenoids as the main type, with 64 compounds; sesquiterpenoids; and tetraterpenoids. Moreover, flavonoids were remarkably revealed with 22 compounds. However, chemicals such as alkaloids, saponins, steroids, and coumarans were marginally reported (Figure 3).

Table 3. *Bryonia* species in vivo/in vitro applications.

Ailments/ Activities	*Bryonia* Species (Family/Part)	Product	[A] Model/Strains	[B] Inhibitory Assay	Dosage	Control (Negative ⊖/Positive ⊕)	Effects	Ref.
In vitro assays								
Anti-Oxidant	*B. dioica* fruits, leaves, stems, flowers, roots	Methanolic/ethanolic extract	DPPH, RP, inhibition of B-carotene bleaching, inhibition of lipid peroxidationTBARS		1 mg/mL	Extract	An antioxidant effect	[32,34]
	B. alba roots	N-hexane, ethylacetate (EtOAc), methanol (MeOH)	DPPH, ABTS, FRAP, and hydroxyl radicalscavenging assay		0.01 mg dw/mL		EtOAc extract showed strong DPPH and ABTS radicalscavenging activity	[13]
	B. alba leaves, aerial parts	Flavonoids (lutonarin, saponarin, isoorientin, isovitexin)	L012 substrate (probe)	Horseradish peroxidase (HRP)-catalyzed oxidation assay	2 and 100 lg/mL	Enzyme alone enzyme and probe	Inhibition ofthe peroxidase-catalyzed reactions showed significant antioxidant activity, proved to pass through cell membranes and to exhibit their antioxidant/antiradical effect	[14,17]
			Myeloperoxidase	Direct MPO assay		Buffer DMSO		
			Neutrophils	Effects on the total ROS produced by PMA-activated neutrophils		Non-PMA-activated cells		
			HL-60	Effects on the ROS produced by PMA-activated HL-60 monocytes		Non-activated cells		
			SNPAC EPR		1 mg/mL		An antioxidant effect	
Antibacterial	*B. dioica* roots, fruits	Lipid fraction	*E. coli*, *S. typhimurium* *E. faecium*, *S. agalactiae*, *S. aureus*	Disk diffusion method according to NCCLS method inhibition zone	15 uL	Ampicillin	Inhibited the growth of all the test bacterial strains	[37]
	B. dioica leaves	Ethanolic extract	*E. coli*, *S. aureas*, *K. pneumoniea*, *S. typhi*, *P. aeruginosa*, *P. valgaris*	Well diffusion assay	200 (mg mL^{-1})		Antimicrobial activity against three Gram-negative microorganisms *E. coli*, *K. pneumoniea*, and *P. valgaris*.	[33]
Anti-Plasmodial	*B. alba* aerial parts	Methanolic extract	Plasmodium falciparum strains: 3D7 and W2	Activity of the plasmodial lactate dehydrogenase (pLDH) at 630 nm	0.8 and 100 ug/mL	Infected and uninfected erythrocytes	No cellular toxicity on the parasitic strains used	[14]
Anti-proliferative	*B. aspera* roots	Hydro-ethanolic	HN-5 and Hela cells	MTT assay	12.5 to 500 µg/mL		Decreased cell viability in Hela and HN-5 cell lines in a concentration- and time-dependent manner	[30]
	B. cretica roots	Triterpene glycosides, bryoniosides A and B	Humanleukemia U937 cells	Cytotoxicity assay	9.2 and 16 nM 72 h		Inhibition of cell proliferation	[31]
	B. cretica roots	Isocucurbitacin D (MeOH)	HT1080 cells	MTT assay	1 uM	Positive control Cucurbitacin E	Cytotoxic effects with the disruption of the target protein cofilin	[31]

Table 3. *Cont.*

Ailments/ Activities	*Bryonia* Species (Family/Part)	Product	[A] Model/Strains	[B] Inhibitory Assay	Dosage	Control (Negative ⊖/Positive ⊕)	Effects	Ref.
In vitro assays								
Cancer/Tumor	*B. alba* roots	23, 24-dihydrocucurbitacin D (dhc D) Ethanol	Cancer cells A-549, COLO 205, SK-MEL-2, L121O	Cytotoxicity test			Antitumor effect on tumor cells	[49]
	B. dioica roots	Bryoniosides, cucurbitacins, cucurbitacin A, cucurbitacin G methanolic extract	In vitro B16F10 melanoma cancer cells	MTT assay Apoptotic effects			Increasing number of cells that express a block in cell cycle progression in the sub-G1phase, followed by cell death induced by apoptosis, anti-melanoma effects by inhibiting cell migration, and invasion through the FAK and Srcsignaling pathways	[48]
	B. dioica roots	Methanolic extract Cucurbitaneglycosides	EBV-EA activation Rajicells (virus nonproducer)	Method of probit-graphic interpolation	1 × 10 mol ratio/TPA	MeOH-$CHCl_3$-H_2O	Deglycosylation enhances the inhibitory effects on EBV-EA activation (anti-tumor)	[36]
	B. dioica roots	Aqueous extract	Burkitt's lymphoma BL41 cells Propidium iodide (PI) staining of cell DNA	Corroborative assays Flow cytometry analysis of dot-blot light scatter profiles	250 to 500 ug/mL	Untreated cells	Inducesapoptosis in Burkitt's lymphoma cells line BL41 by triggering the mitochondria-mediated pathway (exp: activation of caspase-9 and -3 the cleavage of PARP and degradation of PUMA)	[28]
	B. aspera aerial parts	Methanolic	NALM-6 and REH cell lines	MTT assay	200–300 uL/mL		Cytotoxic effect causing apoptosis induction	[45]
	B. aspera roots	Hydro-ethanolic extract	HN-5 and Hela cell lines	Apoptosis assay	12.5–100 µg/mL 48 h	Cells + Dulbecco's modified Eagle's medium (DMEM) Normal cells	Cell death is involved in B. aspera-induced toxicity in Hela and HN-5 cell lines	[30]
	B. aspera roots	Neocucurbitacin C and 7β-hydroxy dihydrocucurbitacin D chloroform extract	Cancer cell lines (MCF7, HepG2, and WEHI) and normal cells MDBK	MTT assay	<50 µg/mL	5-fluorouracil and tamoxifen Non-treated cells	Strongly reduced growth of cancer cells	[46]
Cytotoxicity activity	*B. alba* leaves	Flavonoids (lutonarin, saponarin, isoorientin, isovitexin)	A549, HeLa, WI38, neutrophils, HL-60 cells	Cell viability		Non-treated cells	Very low toxicity or absence of toxicity of the tested samples	[17]
	B. alba aerial parts	Methanolic extract	A549, HeLa, WI38	Cytotoxicity assay	100 ug/mL	-Non-treated cells + Camptothecin	No cellular toxicity	[14]
	B. alba roots	Aqueous and methanol extracts	Human normal (lymphocytes) (HeLa and Caco-2) cells	Comet assay			No genotoxic effects	[50]
	B. dioica	Aqueous extract	BL41 cells	MTT assay	250–500 ug/mL		Cytotoxicity effect	[28]

Table 3. *Cont.*

Ailments/ Activities	*Bryonia* Species (Family/Part)	Product	[A] Model/Strains	[B] Inhibitory Assay	Dosage	Control (Negative ⊖/Positive ⊕)	Effects	Ref.
In vivo assays								
Inflammation	*B. dioica* roots	Glycosides	Female ICR mice	TPA-Induced Inflammation	1 mg per ear	MeOH-$CHCl_3$-H_2O	Inhibitory effects against TPA-induced inflammation Anti-tumor	[36]
	B. alba roots	N-hexane, ethylacetate (EtOAc), methanol (MeOH)	Swiss albino mice	Carrageenan-induced hind paw edema model	0.1 mg/kg	25 µL of saline PC	EtOAc extract showed a statistically significant anti-inflammatory activity in a carrageenan-induced hind paw edema model and an acetic-acid-induced increase in capillary permeability	[13]
				Acetic-acid-induced increase in capillarypermeability (Whittle method)	0.2 mL/20 g			
Diabetes	*B. dioica* roots	Aqueous extract	n5-STZ diabetic rats (Wismar)	Acute toxicity	30 mg/kg, i.p/21 days	Non-diabetic (5 mL/kg b.w./day of saline solution NaCl 9‰; i.p.); diabetic (5 mL/kg b.w./day of saline solution NaCl 9‰; i.p.)	Significantly decreased the level of serum glucose with 64% reductions. The body weight as well as serum levels of total cholesterol, triglycerides, and urea were markedly reversed secondary to subacute administrationof the aqueous extract. Changes in the weight of internal organs were restored to normal by the prolonged effect of the BDRaq extract treatment. The BDRaq extract appeared to have maximum antidiabetic activity in normalizing all studied parameters during the acute and subacute treatments	[39]
	B. multiflora		Wistar albino male rats	Acute toxicity test	100, 200 and 400 mg/kg	Citrate buffer STZ	Prevented damage withliver, kidney, and pancreasamelioration in the functioning of the betacells.	[40]
Hepatotoxicity	*B. dioica* Leaves	Ethanolic extract	Albino male rats	CCL4-induced hepatic damage	250 mg/kg	Saline Ccl4	Protection against the toxic effects of CCL4, hepatoprotective effect	[29]
Anti-nociceptive	*B. alba* Roots	N-hexane, ethylacetate (EtOAc), methanol (MeOH)	Swiss albino mice	P-benzoquinone-induced abdominal constriction Tail flick test	0.1 mg/kg	Vehicle/aspirin Morphine	EtOAc extract displayed antinociceptive activity in the p-benzoquinone-induced writhing mouse model Marked anti-inflammatory effects, with 50% inhibitory doses (ID50) of 0.2–0.6 mg None of the extracts showed any activity in the tail flick test	[13]
SARSCoV-2 infections	*Bryonia alba*	Ethanolic extract	Gallus gallus embryo	Induced pathogenesis assay	10 µg/mL	Alcohol (70%)	Upregulation of IFN-α, IFN-ß, and TGF-ß by Delta SARS-CoV-2 spike protein RBD antigen	[38]

Table 3. *Cont.*

Ailments/ Activities	*Bryonia* Species (Family/Part)	Product	[A] Model/Strains	[B] Inhibitory Assay	Dosage	Control (Negative ⊖/Positive ⊕)	Effects	Ref.
In vivo assays								
Polycystic ovary syndrome	*B. dioica*	Methanolic extract	Immature female Wistar rats	DHEA antiandrogenic assay	30 mg/kg/day for 28 days	Saline Metformin	Protective effect on PCOS rats and normalized the hormones, glucose, LDL, and LDL/HDL ratio, improvement effect on the symptoms and markers of PCOS and fertility	[41]
Toxicity	*B. dioica* Roots	Aqueous extract	Male mice	Acute/subacute oral toxicity	250–1000 mg/kg 62.5–250 mg/kg	Distilled water	Dose higher than 250 mg/kg was shown to be toxic for mice in acute toxicity Dose up to 250 mg/kg was shown to be safe for animals in subacute toxicity	[15]
	B. alba Leaves	Flavonoids (lutonarin, saponarin, isoorientin, isovitexin)	Zebrafish larvae	In vivo toxicity assay		25 embryos not treated	No changes in the parameters were noticed within the 72 h, similar to the ones of the negative control Absence of zebrafish toxicity was confirmed	[17]
	B. alba Aerial parts	Methanolic extract	Zebrafish (Danio rerio)	In vivo acute toxicity	0.1–100 ug/mL	Non-treated larvae	Lack of toxicity	[14]
Cancer	*B. alba* Roots	23, 24-dihydrocucurbitacin D (dhc D) Ethanol	ICR mice sarcoma 180 ascites tumor cells	Antitumoric test	5 to 10 mg/kg 60 days	0.2% ethanol + saline Sarcoma 180 + saline	Antitumor effect	[49]
	B. dioïca Root	Bryoniosides, cucurbitacins, cucurbitacin A, cucurbitacin G Methanolic extract	Balb/c in mice	Apoptotic effect	50 mg M/kg/d (for 28 days)	B16F10-injected mice treated only with PBS	Cell death induced by apoptosis anti-melanoma effects in vivo by inhibiting cell migration and invasion through the FAK and Srcsignaling pathways	[48]

[A] HN-5: head and neck squamous cell carcinoma, Hela: cervix adenocarcinomacell lines, ICRmice: mice from the Institute of Cancer Research, HL-60: human leukemia cells, HT1080: fibrosarcoma cells, A549: lung cancer cells, WI38: fetal lung fibroblast cells, NALM6: human B-cell precursor leukemia cell line, REH: non-B acute lymphoblastic leukemia cell line, MDBK: Madin–Darby bovine kidney, EBV-EA: Epstein–Barr virus earlyantigen. [B] DPPH: diphenyl-2-picrylhydrazyl radical scavenging, RP: reducing power, TBARS: inhibition of lipid peroxidation using thiobarbituric-acid-reactive substancesin brain tissue homogenates, ABTS: [2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonate)] radicalscavenging assay, FRAP: ferric-reducing antioxidant power, PMA: phorbol-12-myristate-13-acetate, SNPAC: silver nanoparticle antioxidant capacity, EPR: electron paramagnetic resonance, TPA: 12-O-tetradecanoylphorbol-13-acetate, DHEA: dehydroepiandrosterone, CCl4: carbon tetrachloride.

Table 4. Phytochemical compounds identified in *Bryonia* species.

Compounds	Species	Plant Part	Area	Extract [1]	Analysis [2]	Ref.
Primary metabolites						
Elements						
Fe, Si, P, Al, Mn, Mg, Pb, Ni, Mo, Ca, Cu, Zn, Na, K, Sr, Co, Cd, As, and Hg	*B. dioica* *B. alba*	Root	Ukraine	Ash	AAS	[51]
Sugars						
Fructose	*B. dioica*	Fruit	Portugal	MeOH		[34]
Glucose						
Sucrose						
Trehalose						
Raffinos	*B. alba* *B. multiflora*	Root	Ukraine	dH_2O	GC/MS	[52]
Ribose						
Rhamnose						
Arabinose						
Xylose						
Fucose						
Mannose						
Galactose						
Vitamins						
α-Tocopherol	*B. dioica*	Fruit	Portugal	MeOH		[34]
β-Tocopherol						
γ-Tocopherol						
δ-Tocopherol						
Ascorbic acid						
Proteins/a.a						
Lectin	*B. dioica*	Root				
Bryodiofin						
Bryodin						
N4-(2-hydroxyethyl)-L-asparagine	*B. dioica*					
Other a.a	*B. alba* *B. mutiflora*	Root	Ukraine	dH_2O, MeOH	HPLC	[34,53]
Fatty acids						
Methyl jasmonate	*B. dioica*					
α-linolenic acid	*B. dioica*					
Trihydroxyocdecadeinoic acids	*B. multiflora* *B. alba*	Root				[38]
Bryonolicacid (Ba) 3β-Hydroxy-D: C-Friedoolean-8en-29-Oic acid						
Other essential oils	*B. dioica*	Fruit, aerial parts, root	Tunisia	Oil	GC-FID/GC–MS	[37]
Secondary metabolites						
Terpenoids (Triterpenoid)						
Dihydrocucurbitacin B (DHCB)	*B. cretica*	Root	Egypt	EtOH	HPLC	[31]
	B. aspera		Iran	TCM		[46]
Dihydrocucurbitacin D (DHCD)	*B. alba*	Root	Armenia	MeOH	H/C-NMR, UV, MS	[46,49]
	B. aspera		Iran	TCM		
Dihydrocucurbitacin E (DHCE)	*B. cretica*	Root	Egypt	EtOH	HPLC	[31]
Hexanorcucurbitacin D	*B. cretica*	Root	Egypt	EtOH	HPLC	[31]

Table 4. *Cont.*

Compounds	Species	Plant Part	Area	Extract [1]	Analysis [2]	Ref.
Secondary metabolites						
Terpenoids (Triterpenoid)						
Cucurbitacin B(CuB) (Amarine)	*B. multiflora*	Root	Turkey	MeOH	HPLC	[54]
	B. verrucosa			TCM		
	B. cretica					
Cucurbitacin G	*B. cretica*	Root	Egypt	MeOH	NMR, X-ray crystallography	[27]
Cucurbitacin H	*B. cretica*	Root	Egypt	MeOH	NMR, X-ray crystallography	[27]
Cucurbitacin I (Elatericin B)	*B. alba*	Root	Turkey	MeOH	HPLC	[27,31,36,54]
	B. multiflora			TCM		
	B. dioica			MeOH		
	B. verrucosa		Germany	EtOH	C-Sephadex LH-20	
	B. cretica		Egypt	MeOH	HPLC	
Cucurbitacin D (Elatericin A)	*B. alba*	Root		EtOH	HPLC	[31,54]
	B. verrucosa					
	B. cretica		Egypt	MeOH		
Cucurbitacin E (α-Elaterin)	*B. alba*	Root			HPLC	[31,54]
	B. verrucosa					
	B. cretica	Root	Egypt	EtOH		
Cucurbitacin J	*B. alba*	Root			HPLC	[31,54]
	B. dioica					
	B. cretica		Egypt	EtOH		
Cucurbitacin K	*B. alba*	Root				[36,54]
	B. dioica	Root				
Cucurbitacin L	*B. alba*	Root		MeOH	H/C-NMR TLC, C- Sephadex LH-20	[23,36,46,54,55]
	B. melanocarpa		Uzbekistan			
	B. dioica		Germany			
	B. cretica					
	B. aspera		Iran	TCM		
Cucurbitacin S	*B. dioica*					
Bryoamaride	*B. melanocarpa*	Root	Uzbekistan	MeOH	H/C-NMR TLC, C/H NMR	[23,36,55]
	B. dioica		Japan			
Isomultiflorenol	*B. melanocarpa*					
bryocoumaricacid	*B. dioica*					
3a-hydroxy-multiflora-7, 9 (11)-dien-29a-oic acid	*B. dioica*					
Arvenin IV	*B. alba*					
Isocucurbitacin G	*B. cretica*	Root	Egypt	MeOH	NMR, X-ray crystallography	[27]
Isocucurbitacin H	*B. cretica*	Root	Egypt	MeOH	NMR, X-ray crystallography	
Isocucurbitacin D	*B. cretica*	Root	Egypt	MeOH	NMR, X-ray crystallography	

Table 4. *Cont.*

Compounds	Species	Plant Part	Area	Extract [1]	Analysis [2]	Ref.
Secondary metabolites						
Terpenoids (Triterpenoid)						
Iso Dihydrocucurbitacin D	*B. aspera*	Root	Iran	TCM MeOH	2D NMR	[26,46]
Epi-Iso Dihydrocucurbitacin B						
7β-hydroxy dihydrocucurbitacin D						
25-Oglucosyl Dihydrocucurbitacin D						
2-O-Glucosyl Dihydrocucurbitacin D						
4-Hydroxy-N-(2-hydroxyethyl)-benzamide (bryonamide A)						
4-Hydroxy-3-methoxy-N-(2-hydroxyethyl)-benzamide (bryonamide B)						
Bryonolic acid	*B. aspera* *B. melanocarpa*	Root	Iran	TCM MeOH	2D NMR	[26,46]
Tirucalla-5, 24-dien-3b-ol	*B. dioica*	Root		MeOH		[36]
25-O-acetyl bryoamaride	*B. dioica*	Root	Germany	MeOH	C-Sephadex LH-20	
Bryodiosides A	*B. dioica*	Root	Japan	EtOH	C-Sephadex LH-20	
Bryodiosides B						
Bryodiosides C						
Bryodulcoside	*B. dioica*	Root	Germany	MeOH		
Bryonoside	*B. dioica*	Root	Japan	EtOH	C-Sephadex LH-20 FDMS, H/C NMR	
Bryoside	*B. dioica*	Root			Chemical, FDMS, H/C NMR	
Cucurbitacin I 2-O-â-D-glucopyranoside	*B. dioica*	Root	Germany	MeOH	C-Sephadex LH-20	
10α-cucurbitadienol	*B. dioica*	Root	Japan	ACE -MeOH	HPLC	
(24R)-24-ethyl-5a-cholest-7-en-3b-ol	*B. melanocarpa*					
B-sitosterol-3-O-glucoside	*B. cretica*					
Stigmasta-7E, 24 (28)-dien-3b-ol	*B. melanocarpa*	Root				
4a-methyl stigmasta-7E, 24 (28)-dien-3b-ol						
(24R)-24-ethyl-5a-cholest-7-en-3b-ol 3-O-b-D-glucopyranoside						
10 Is 2-O-B-D-glucopyranoside						
Elaterinide	*B. dioica*	Root	Germany Algeria	MeOH	C-Sephadex LH-20	[28,36]
Tetrahydrocucurbitacin	*B. dioica*	Root	Algeria			[36]
Bryonioside A	*B. dioica* *B. cretica*	Root	Japan Egypt	EtOAc EtOH	HPLC	[26,36]
Bryonioside B	*B. dioica* *B. cretica*	Root	Japan Egypt	EtOAc EtOH	HPLC	[26,36]

Table 4. *Cont.*

Compounds	Species	Plant Part	Area	Extract [1]	Analysis [2]	Ref.
Secondary metabolites						
Terpenoids (Triterpenoid)						
Bryonioside C	*B. dioica*	Root	Japan	EtOAc of MeOH	HPLC	[36]
Bryonioside D						
Bryonioside E						
Bryonioside F						
Bryonioside G						
Cabenoside D	*B. dioica*	Root	Japan	EtOAc	C/H NMR	[36]
Bryodulcosigenin	*B. dioica*	Root	Japan	EtOAc	C/H NMR	
Bryosigenin	*B. dioica*	Root	Japan	EtOAc	C/H NMR	
Bryogenin	*B. dioica*					
22-deoxocucurbitosides A	*B. alba* *B. multiflora*	Root		EtOH		
22-deoxocucurbitosides B	*B. alba*			EtOH		
22-deoxocucurbitosides D	*B. multiflora*	Root				
22-deoxocucurbitacin D	*B. alba*			EtOH		
Neocucurbitacin C	*B. aspera*	Root	Iran	TCM	2D NMR	[26,46]
Terpenoids (Sesquiterpenoids)						
Maaliol	*B. dioica*	Root	Morocco	dH_2O	GC–MS	[15]
Saponins						
Brydiosides A	*B. dioica*	Root	Algeria			[26,28,49]
Brydiosides B						
Brydiosides C						
Steroids						
Delta7-stigmastenol	*B. dioica*					
Flavonoids						
Saponarin	*B. dioica* *B. alba*	Root Leaves/aerial part	Algeria Romania	MeOH	HPLC–DAD, MS/NMR	[14,17,28,39]
Isovitexin	*B. alba*	Aerial parts	Romania	MeOH	HPLC–DAD	[14,17]
Vitexin						
Vicenin	*B. dioica*					[11]
Lutonarin	*B. alba*	Leaves/aerial parts	Romania	MeOH	HPLC–DAD, MS/NMR	[14,17]
Isoorientin	*B. alba*	Leaves/aerial parts	Romania	MeOH	HPLC–DAD, MS/NMR	[14,17]
5, 7, 4′-trihydroxy flavone 8-Cglucopyranoside	*B. alba*					
Alliaroside	*B. dioica*					

Table 4. *Cont.*

Compounds	Species	Plant Part	Area	Extract [1]	Analysis [2]	Ref.
			Flavonoids			
Apigenin-C-Hexoside-O-Hexoside	*B. dioica*	Fruit	Portugal	EtOH	HPLC–DAD–ESI/MS	[56]
Apigenin-6-C-Glucoside-8-C-Glucoside						
Apigenin-6-C-Glucoside-7-O-Glucoside						
Apigenin-C-Hexoside-O-Hexoside						
Apigenin-6-C-Glucoside (Isovitexin)						
Quercetin-3-O-Neohesperidoside						
Quercetin-O-Rhamnosyl-Pentoside						
Quercetin-O-Rhamnosyl-Rhamnoside	*B. dioica*	Root				[12]
Quercetin-O-Hexoside 8						
Kempferol 3,7-Di-O-Rhamnoside						
Kaempferol-O-Rhamnosyl-Hexoside-O-Rhamnoside						
Kaempferol-3-O-Neohesperidoside						
Kaempferol-O-Pentosyl-Rhamnoside						
Kaempferol-3,4′-Di-O-Rhamnoside						
			Alkaloid			
Bryonicine	*B. alba*	Leaves		EtOH		[38,57]
			Coumarans			
Coumaran	*B. dioica*	Root	Morocco	dH_2O	GC–MS	[15]
			Pigments			
Chlorophyll A	*B. dioica*	Fruit	Portugal	MeOH		[34]
Chlorophyll B						
Lycopene						
β-carotene	*B. dioica*	Fruit/shoot	Portugal Spain	MeOH		[34,58]
Lutein						
Neoxanthin	*B. dioica*	Shoot	Spain		HPLC–PDA	[58]
Violaxanthin						

[1] EtOH: ethanolic extract, EtOAc: ethyl acetate extract, MeOH: ethanol extract, TCM: chloroform extract, dH_2O: aqueous extract; [2] HPLC: high-performance liquid chromatography, GC–MS: gas chromatography–mass spectrometry, H/C-NMR: proton/carbon nuclear magnetic resonance, GC-FID: gas chromatography with flame ionization detection, HPLC–PDA: high-performance liquid chromatography–photodiode array detection, HPLC–DAD–ESI/MS: high-performance liquid chromatography–diode array detection–electro-spray ionization mass spectrometry, 2D NMR: two-dimensional nuclear magnetic resonance spectroscopy, FDMS: field desorption mass spectrometry, TLC: thin-layer chromatography, UV: ultraviolet, MS: mass spectrometry.

- Terpenoids

Terpenoids are considered the largest phytochemical class widely distributed in almost all plants. According to their carbon units, terpenoids include monoterpenes, diterpenes, triterpenes, sesquiterpenes, and sesterpenes [59]. Triterpenoids were found to be abundant in *Bryonia* species. Among them, cucurbitacins are considered the most important triterpenoids of the *Bryonia* species. Cucurbitacins, highly oxygenated triterpenoids with a 19-

(10→9β)–abeo–10α–lanost–5–ene ring skeleton and 5,(6) –double bond, are often tetracyclic and highly unsaturated [60]. Actually, cucurbitacins E, B, I, D, J, K, and L, dihydrocucurbitacins E and B, and tetrahydrocucurbitacin I were identified in *Bryonia* roots, with some differences due to the harvest period, geographical location of the plant, and extraction methods [61]. Sallam et al. (2010) isolated two cucurbitacins, isocucurbitacins G and H, from *Bryonia* roots [27]. Earlier, other triterpenoids, namelybryonoside and bryoside, were isolated [62]. Ukiya et al. (2002) isolated ninetriterpene glycosides: bryoniosides A−G, cabenoside, and bryoamaride [36] (Figure 4).

On the other hand, three tetraterpenoids (lycopenetetra, chlorophyll A, and β-carotene) along with a sesquiterpenoid (Maaliol) have been reported in methanolic and aqueous extracts from *B. dioica* species (Figure 5).

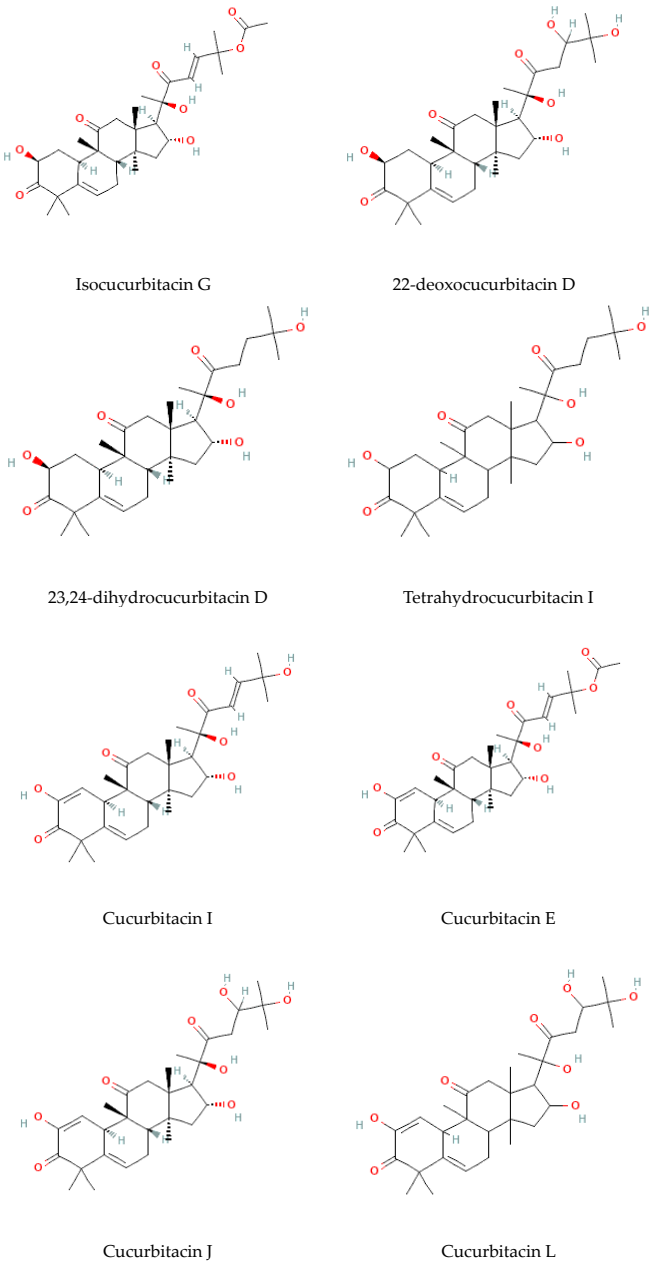


Figure 4. *Cont.*

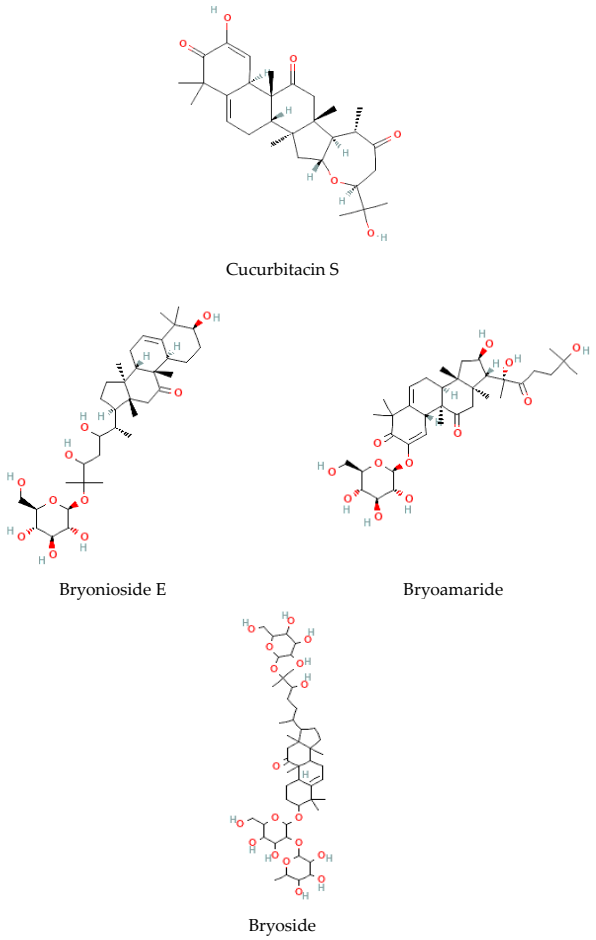


Figure 4. Triterpenoid-type molecules isolated from *Bryonia* genus.

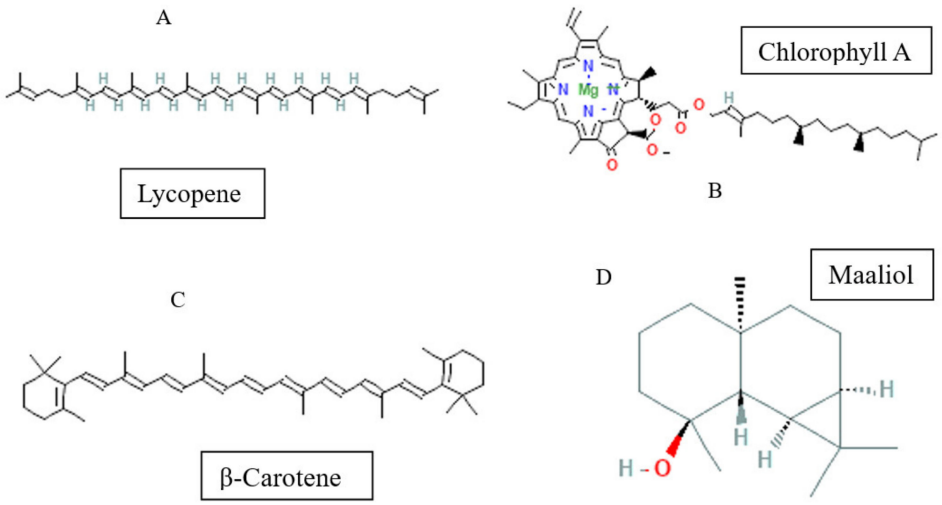


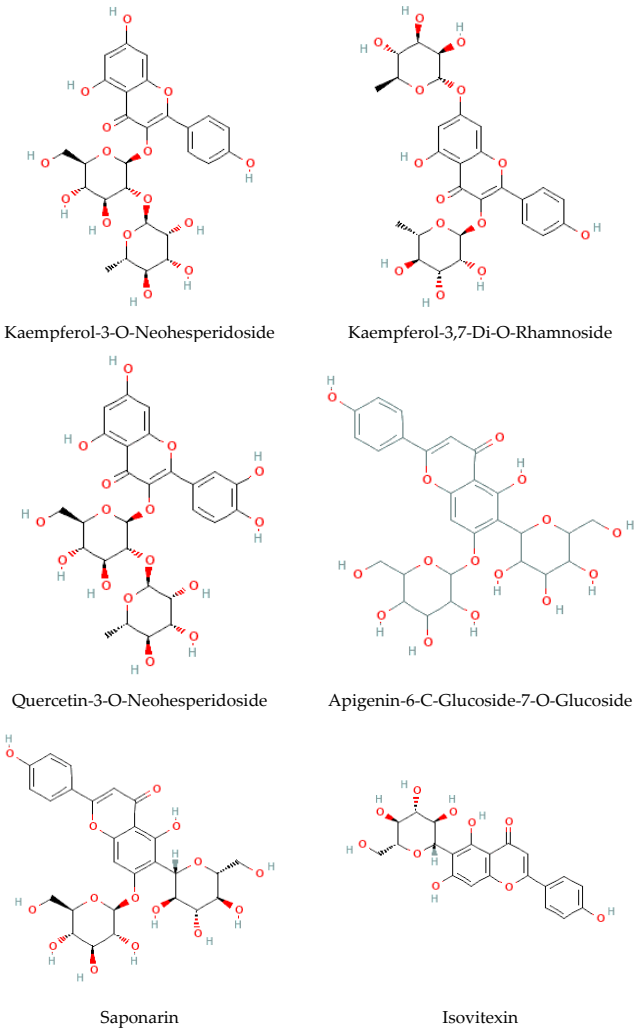
Figure 5. Tetraterpenoid/sesquiterpenoid-type molecules isolated from *Bryonia* genus ((**A**–**C**) tetraterpenoids and (**D**) sesquiterpenoid).

- Flavonoids

Considered the second major phytochemical group in the genus *Bryonia*, 23 flavonoids (Table 4, Figure 6) have been isolated from this genus, including 9 flavanols and 11 flavones, during the latest 22 years. Lelciu et al. (2019) identified four flavonoids in the crude extract of the aerial parts of *B. alba* [17]. These flavonoids were lutonarin, saponarin, isoorientin, and isovitexin. Earlier, saponarin and vicenin-2 were reported in *B. dioica* [63]. Moreover,

Barreira et al. (2013) reported the presence of both O- and C-glycosides of flavonoids in the methanolic extract of *B. dioica* fruits. Actually, they identified O- and C-glycosides of two flavonols—quercetin (Quercetin-3-O-neohesperidoside, Quercetin-O-rhamnosyl-pentoside, Quercetin-O-rhamnosyl-rhamnoside, Quercetin-O-hexoside) and kaempferol (Kaempferol-O-rhamnosyl-hexoside-O-rhamnoside, Kaempferol-3-O-neohesperidoside, Kaempferol-O-pentosyl-rhamnoside, Kaempferol-O-pentosyl-rhamnoside, Kaempferol-3,4′-di-O-rhamnoside)—and one flavone: apigenin (Apigenin-6-C-glucoside, Apigenin-C-hexoside-O-hexoside, Apigenin-6-C-glucoside-8-C-glucoside, Apigenin-6-C-glucoside-7-O-glucoside, Apigenin-C-hexoside-O-hexoside) [56].

Among the flavonols, five kaempferol and four quercetin flavonols were revealed completely in the *B. dioica* roots with no reports onthe extraction method or even the detection method. Nevertheless, Quercetin-3-O-Neohesperidoside and Quercetin-O-Rhamnosyl-Pentoside were found in an ethanol extract of *B. dioica* fruit using HPLC–DAD–ESI/MS. Likewise, the flavone apigenin (Apigenin-C-Hexoside-O-Hexoside, Apigenin-6-C-Glucoside-8-C-Glucoside, Apigenin-6-C-Glucoside-7-O-Glucoside, Apigenin-C-Hexoside-O-Hexoside, Apigenin-6-C-Glucoside) was detected. In addition, both *B. alba* and *B. dioica* leaves showed other type of flavonoids such as saponarin, lutonarin, and isoorientin via different methods (HPLC–DAD and MS/NMR). Gholivand and Piryaei (2012) reported that flavonoids were obtained from *B. dioica* flowers, leaves, and stems using several extracts (polar and nonpolar) [32]. Similarly, amethanolic extract of *B. alba*'s aerial parts showed the presence of lutonarin, saponarin, isoorientin, and isovetexin [14].



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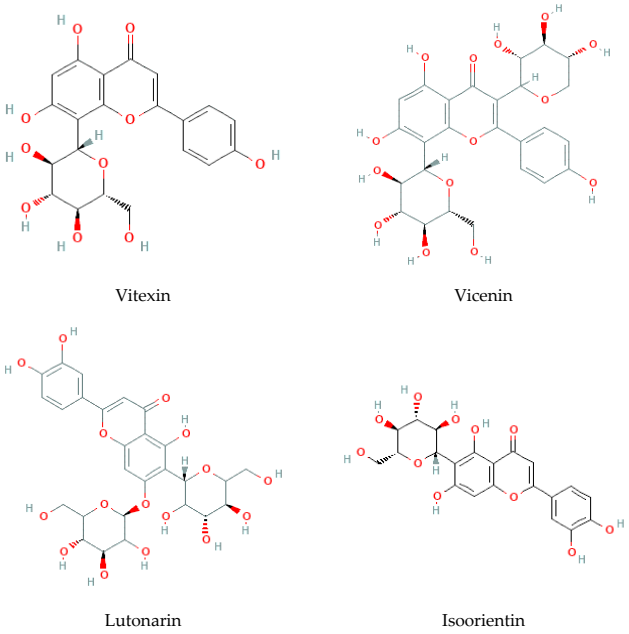

Figure 6. Flavonoid-type molecules isolated from *Bryonia* genus.

- Alkaloids

Few data on the alkaloidcomposition of *Bryonia* L. have been reported. One of the alkaloid compounds mentioned was bryonicine, extracted from the leaves of *B. alba* through maceration with ethanol [38,57].

- Fatty acids

Methyl jasmonate, α-linolenic acid, trihydroxyocdecadeinoicacids, and Bryonolic Acid (Ba) 3β-Hydroxy-D:C-Friedoolean-8en-29-Oic Acid are the fatty acids found and reported in previous studies on *B. multiflora*, *B. alba*, and *B. dioica* [37] (Figure 7).

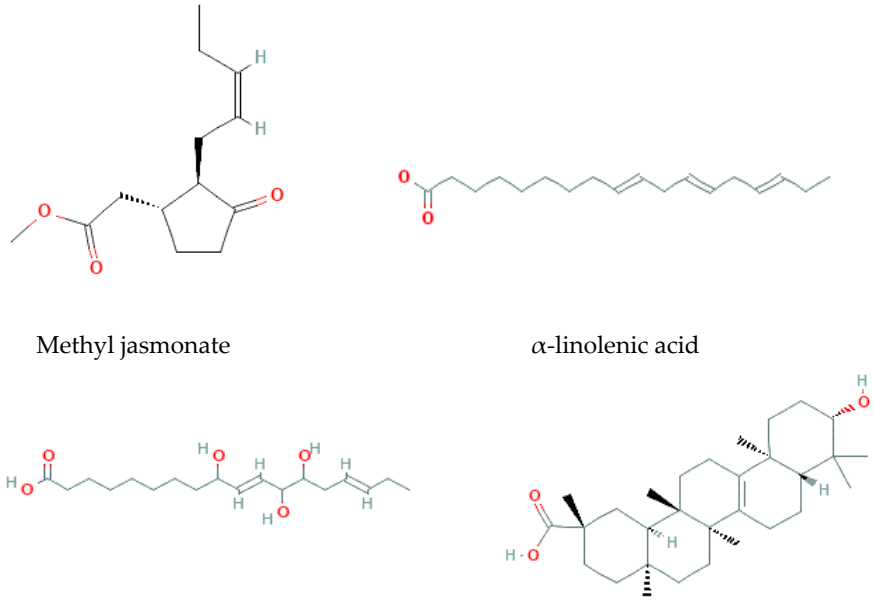

Figure 7. Fatty acids isolated from *Bryonia* genus.

- Other compounds:

In particular, *B. dioica* roots were studied and revealed the identification of coumaran in their aqueous extract, beside saponins (brydiosides) and a steroid (Delta7-stigmastenol), for which the details are still unknown (Figure 8). Furthermore, other compounds were reported in the *B. dioica*, *B. alba*, and *B. cretica* species, especially terpenoids as mainly bioactive compounds (Table 4).

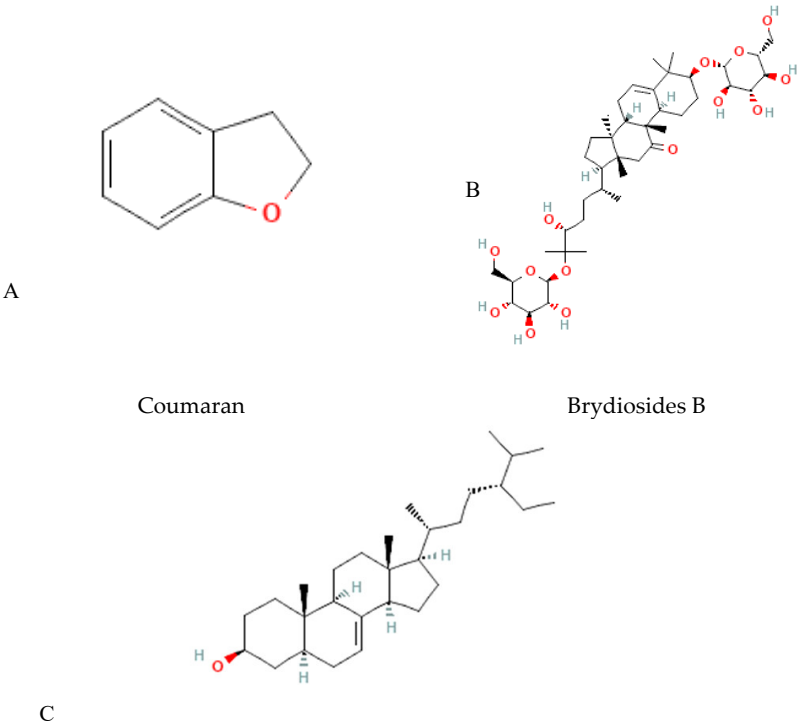

Figure 8. Other molecules isolated from *Bryonia* genus. ((**A**) Coumaran, (**B**) saponin, and (**C**) steroid).

In this review, other compounds, namely C-glycosides, emerged as significant building blocks for many naturally occurring triterpenoids, bryoniosides (Figure 4), and the flavonoid apigenin-6-C-glucoside-7-O-glucoside (Figure 6) [64].These compounds have attracted plenty of attention as bioactive agents, flavor precursors, and detergents, which are either extracted from plant materials or chemically synthesized [65]. However, these methods suffer from low yields as a matter of their stability and functionality. Thus, various approaches have been developed for the formation of C-glycosidic usingimproved biocatalytic processes involving GT enzymes [65]. A previous study focused on developing efficient protocols for the synthesis of 1,2-annulated glycosides. The study reported the synthesis of sugar-fused indolines via C(sp2)–H/NeH activation starting from 2-nitroglycals using palladium-catalyzed CeH amination reactions [66]. Moreover, another study adopted the Prins cyclization approach using pivaloyl protection to form 2-deoxy-3,4-fused C-aryl/alkyl glycosides [67]. These strategies succeeded in synthesizing a protected C-glycoside compound viadecomposition from the first step.

Furthermore, among the identified phytochemicalsin *Bryonia*, a few compounds were isolated as pure bioactive molecules from different genera and investigated for their biological effects (Table 5). Most of them, such as isoorientin, isovitexin, cucurbitacin A, B, C, and D, and 23,24-dihydrocucurbitacin D, exhibited anticancer activity against gastric cancer, lung cancer, and ovarian cancer [68–74]. Moreover, bryoniosides A and B and isocucurbitacin D showed an antiproliferation capacity [31]. Besides their antioxidant properties, other flavonoid compounds, namely lutonarin and saponarin, were considered anti-inflammation agents due to theirinhibition of the phosphorylation of signaling

effectors and the expression of inflammatory mediators, especially tumor necrosis factor (TNF)-α and the inflammatory enzyme cyclooxygenase-2 (COX-2) [75,76].

Table 5. The main bioactive compounds identified in *Bryonia* genus with important bioactivities.

Compounds	Agent against	Effects	Ref.
Lutonarin	Oxidation Inflammation	Inhibition of the peroxidase-catalyzed reactions with significant antioxidant/antiradical effect. Suppression of LPS-induced expression, phosphorylation, and nuclear translocation of NF-κB. Inhibition of LPS-induced upregulation of proinflammatory cytokines IL-6 and TNF-α and of the inflammatory enzymes COX-2 and iNOS.	[14,17,75]
Saponarin	Inflammation	Inhibition of phosphorylation of extracellular signal-regulated kinase (ERK) and p38. Inhibition of both β-hexosaminidase degranulation and phosphorylation of signaling effectors and the expression of inflammatory mediators TNF-α, IL-4, IL-5, IL-6, IL-13, COX-2, and FcεRIα/γ. Inhibition of expression of macrophage-derived chemokine, thymus, and activation-regulated chemokine, IL-33, and thymic stromal lymphopoietin, and the phosphorylation of signaling molecules in TNF-α- and interferon (IFN)-γ-stimulated HaCaT cells. Induction of the expression of hyaluronan synthase-3, aquaporin 3, and cathelicidin antimicrobial peptide (LL-37) in HaCaT cells. Inhibition of factors involved in the inflammatory and allergic responses of RAW264.7, RBL-2H3, and HaCaT cells.	[76]
Bryoniosides A/B	Proliferation	Inhibition of cell proliferation.	[31]
Isocucurbitacin D		Cytotoxic effects with the disruption of target protein cofilin.	[31]
Isoorientin	Cancer	Inhibition of cellmigration by inhibiting activity/expression of MCTs1/4 and MMPs2/9 in human lung cancer cells.	[68]
Isovitexin		Inhibition of cell proliferation and glucose metabolism via downregulating the expression of PKM2 to enhance the antitumor activity of DDP against lung cancer cells and improve DDP-induced immunotoxicity in mice.	[69]
23, 24-dihydrocucurbitacin D		Antitumor effect on tumor cells Suppression of gastric cancer cell proliferation, migration, and invasion through targeting ERK2 and disrupting the Ras/Raf/ERK/MMP9 signaling pathway. Dual transcriptional regulation of LDLR and PCSK9 in HepG2 cells by increasing SREBP2 protein levels and decreasing HNF1α protein levels in the nuclei. Decrease inthe expression of important proteins in the PI3K/Akt/mTOR cascade. Induction of apoptosis in HeLa cells and caused ROS-mediated shifts in the ΔΨm.	[49,74,77,78].
Cucurbitacin A		Inhibition of the expression of key proteins in thePI3K/Akt/mTOR signaling pathway in ovarian cancer cells.	[70]
Cucurbitacin C		Inhibition of growth of cancer-cell-derived xenograft tumors in athymic nude mice and induction of apoptosis.	[72]
Cucurbitacin B		Decrease inthe phosphorylation of TYR-705 in STAT3 and suppression of STAT3 target gene expression, including c-Myc and Bcl-xL in gastric cancer.	[71]
Cucurbitacin D		Inhibition of growth of cervical-cancer-cell-derived orthotopic xenograft tumors in athymic nude mice.	[73]
Cucurbitaneglycosides		Deglycosylation enhances the inhibitory effects on EBV-EA activation (anti-tumor). Moderate anti-tumor activity toward HeLa cell lines.	[36,79]
Neocucurbitacin C		Cytotoxic.	[46]

4. Limitations

Although a systematic process was applied to the research, selection, and analysis of the included studies, there are several limitations to point out. First, the small number

of studies deserves consideration. Also, the selected studies focused on certain species, providing, in general, some biological data. Moreover, most of the included investigations were conducted on species extracts as sources of pharmacological agents and did not consider the isolation of active compounds, whereas some of the selected studies recorded the detected compounds without experimental applications. On the other hand, the lack of in vivo assessments of the toxicity profiles remains a challenge when interpreting the *Bryonia* research. Although previous studies reported the significant anticancer potential of compounds such as cucurbitacins, the molecular mechanisms involved and signaling pathways targeted remain unclear and need to be further investigated. Importantly, in spite of the significant biological activities reported here, no clinical trials have been undertaken to demonstrate the clinical usefulness of such products. However, this systematic review allowed us to summarize the research on particular compounds and identify important pharmacological activities that could be addressed in future research projects.

5. Conclusions

This systematic review documented interesting findings showing the diversity of *Bryonia* species spread across the world, isolated molecules from their different parts, and their therapeutic potential. Here, we found that some species such as *B. dioica*, *B. aspera*, *B. alba*, and *B. cretica* were more studied than other species in the genus due to their traditional uses. These plants maypossess important economic value aseasily cultivable species that represent a large reservoir of chemical components, principally triterpenoids (cucurbitacins and dihydrocucurbitacins). According to most of the previously published papers, this major class, besides flavonoids, especially lutonarin, saponarin, isoorientin, andisovitexin, showed remarkable pharmaceutical properties as antioxidant, anti-inflammatory, and mainly anticancer agents.Although the current report provides a detailed account of the updated information in terms ofvaluable results on taxonomy, geographic distribution, ethnopharmacology, and more on the phytochemical and therapeutic aspects, some limitations regarding the isolation of active compounds, clinical usefulness, and pharmaceutical application of *Bryonia* species should be considered. Therefore, further studies should be focused on identification and clarification of the molecular mechanisms of the biological activities of phytochemicals isolated from *Bryonia* species, in particular from the root parts of both *B. alba* and *B. dioica*. The genus needs more in-depth research to reveal the molecules responsible for these biological activities, which may lead to discovering novel and unique therapeutic molecules.

Author Contributions: B.B. and K.B. contributed equally to the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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