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Review

Traditional Uses, Pharmacology and Phytochemistry of the Medicinal Plant *Flueggea virosa* (Roxb. ex Willd.) Royle

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Abstract: The white berry bush, officially *Flueggea virosa* (Roxb. ex Willd.) Royle is a medicinal plant distributed throughout tropical areas and traditionally used in Africa, India and China. Root decoctions are used to treat abdominal pain, whereas extracts from the aerial parts serve to treat liver and urinary diseases, inflammatory pathologies and diabetes, among other pathologies. Plant extracts have revealed antiparasitic, antimicrobial, antiepilepsy, antidiabetic, anticancer and analgesic effects. Three main categories of phytochemicals were isolated from *F. virosa*: polyphenols, with the lead product bergenin; terpenoids, such as the flueggenoids and related podocarpane-type diterpenoids; and many alkaloids derived from securinine and norsecurinine. A remarkable feature of *S. virosa* is the production of norsecurinine oligomers, including macromolecular tetramers and pentamers, such as fluevirosinines. The most potent anticancer alkaloid in the family is the dimeric indolizidine flueggine B, which was identified as a potential binder to α/β-tubulin dimer, which is a known target for securinine. This review highlights the diversity of phytochemicals identified from *S. virosa* and the potential therapeutic benefits of dimeric alkaloids. Studies are encouraged to further investigate the therapeutic properties of the lead compounds but also define and finesse the nutritional profile of the edible fruit.

Keywords: alkaloid oligomers; bergenin; *Flueggea virosa*; phytochemicals; *Securinega virosa*; securinine; traditional medicine; tubulin binding

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1. Introduction

The plant genus *Flueggea* (family *Phyllanthaceae*, previously called *Euphorbiaceae*) includes 16 species with a botanically accepted name (Table 1). These plants have a worldwide distribution but they are particularly abundant in tropical areas, ranging from Africa to Asia and Australia [1]. They are mostly shrubs and trees and are usually referred to as bushweeds. The plant genus *Flueggea* was named in honor of the botanist Johannes Flüggé (1775–1816), who was a native of Hamburg (Germany) and the author of the famous monograph on *Paspalum* plants (*Graminum Monographiae* published in 1810).

Several *Flueggea* species are used in traditional medicine. This is the case for *F. suffruticosa* (Pall.) Baill., which is commonly used in traditional Chinese medicine for the treatment of inflammatory ailments, such as rheumatism and lumbago [2], and for *F. leucopyrus* Willd., which is used by folk medical practitioners in Sri Lanka as a decoction to treat cancer [3,4]. Another largely used species is *Flueggea virosa* (Roxb. ex Willd.) Royle (Figure 1; hereafter *F. virosa*) as a leaf decoction to cure lactation problems and sick babies at birth and as a root decoction to cure abdominal pain and other applications. The plant is used to treat various diseases and symptoms in Asia, notably as a folk Chinese medicine for the treatment of eczema and rheumatoid arthritis [5,6]. It is also an important medicinal plant in tropical Africa, used alone or in combination with other plants, for a variety

of purposes, including liver, kidney, urinary and venereal diseases, bile deficiency, testicular inflammation, frigidity, sterility, heavy menstruation, rheumatism and arthritis [7]. The plant has been around for a long time. There is evidence of the use of a digging stick of *F. virosa* dated to ~39,000 years before present by the Stone Age inhabitants in South Africa [8].

Table 1. Accepted names of *Flueggea* species (Phyllanthaceae) [1].

- *Flueggea acicularis* (Croizat) G.L.Webster
- *Flueggea acidoton* (L.) G.L.Webster
- *Flueggea anatolica* Gemici
- *Flueggea elliptica* (Spreng.) Baill.
- *Flueggea flexuosa* Müll.Arg.
- *Flueggea gracilis* (Merr.) Petra Hoffm.
- *Flueggea jullienii* (Beille) G.L.Webster
- *Flueggea leucopyrus* Willd.
- *Flueggea monticola* G.L.Webster
- *Flueggea neowawraea* W.J.Hayden
- *Flueggea schuechiana* (Müll.Arg.) G.L.Webster
- *Flueggea spirei* Beille
- *Flueggea suffruticosa* (Pall.) Baill.
- *Flueggea tinctoria* (L.) G.L.Webster
- *Flueggea verrucosa* (Thunb.) G.L.Webster
- *Flueggea virosa* (Roxb. ex Willd.) Royle

[1] According to https://www.worldfloraonline.org/ (accessed on 15 December 2023).

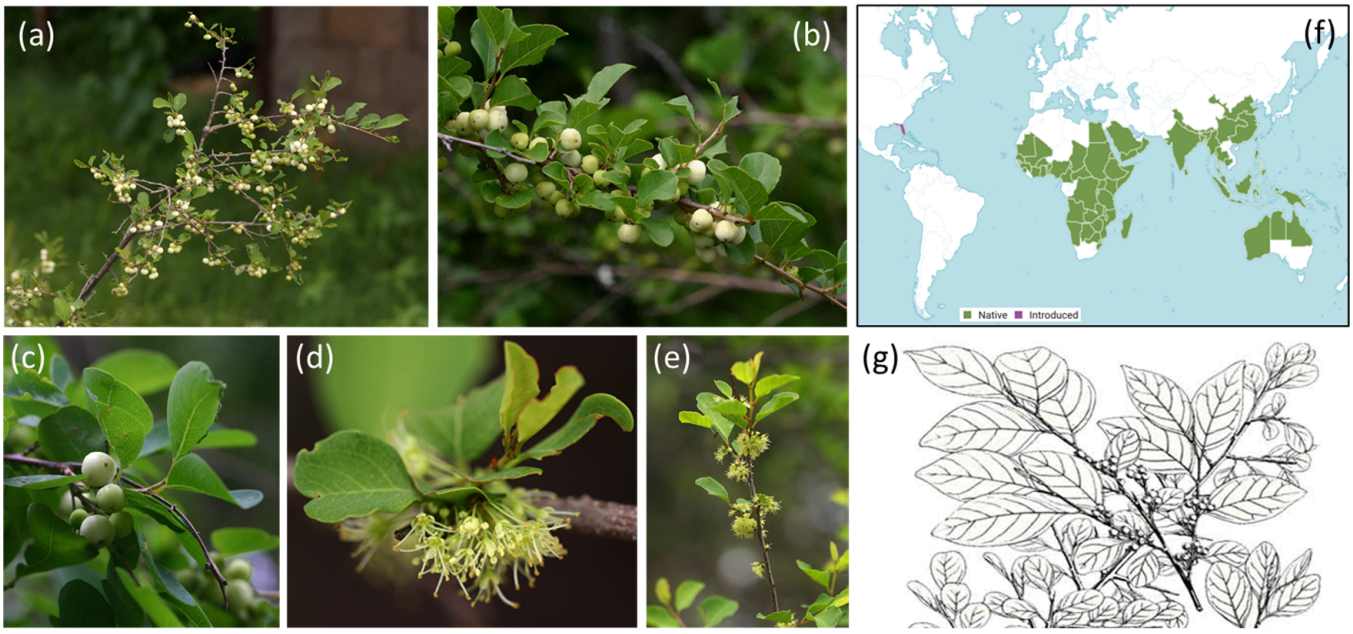

Figure 1. The plant *Flueggea virosa* (Roxb. ex Willd.) Royle, also known as *Securinega virosa* (Roxb. ex Willd.) Baill. (**a**–**e**) Twigs, leaves and fruit of *F. virosa*. (**f**) This *Flueggea* species is mostly distributed in Africa, southeast Asia and Oceania. (**g**) Drawing of the bush.

F. virosa is known as the white berry bush or the Chinese waterberry in English. The given common names vary considerably from one country to another, with more than 50 trivial names identified in >35 countries (Table 2). The diversity of names reflects the common use of the plant in traditional medicine. The complete plastome of the plant is known. It includes 130 genes (for a total of 154,961 bp) with 80 unique protein-coding genes. Phylogenetically, *F. virosa* is close to another medicinal plant, namely, *Phyllanthus emblica* Linn. (amla) [9,10]. *F. virosa* is a dioecious (male and female flowers on separate plants), multi-stemmed, fast-growing, bushy shrub or small tree with small, rounded leaves and tiny, greenish flowers, along with greenish-*white* fruit (Figure 1). The plant is commonly found in the drier parts of the African continent, the Arabian Peninsula, the Indian subcontinent, China (Guangxi, Guangdong, Guizhou, Hubei, Hunan provinces), southeast Asia and northern Australia. It is listed as an invasive species in Florida, USA. *F. virosa* usually grows well in a wide variety of habitats, including forest edges, bushland, grassland, woodland and thickets. In drier areas, it occurs mainly along water courses and in swampy habitats, sometimes on termite mounds and rocky slopes; it is also common in

disturbed localities and fallow land from sea level up to 2300 m altitude. *F. virosa* usually grows up to 4 m tall, with many erect or arching branches. It is generally harvested from the wild, but it is also cultivated for its various useful medicinal values and as an ornamental hedge [11].

Table 2. Vernacular names given to *Flueggea virosa* (and synonyms) [a].

Country (Region or Province)	Vernacular Names (Language)	References
English names	White berry bush, snowberry tree, Chinese waterberry, simpleleaf bushweed, common bushweed.	(a)
Benin (Cotonou, Abomey-Calavi)	Gaagah, tchian tchian, sian sian (Bariba); yéri kalawunfa (Berba); adjaya, gbyihountin, hétré, hounsividjayé, tchaké tchaké (Fon, Goun); koukrinou (Gourmantché); tchamanoudira (Kotokoli); hesré (Watchi); igi agbado, irandjé, wadjidji (Watchi); hesre (Fon)	[12]
Burkina Faso (Ouagadougou) (Niangoloko forest)	Sûgdendaaqa (Mossi), fiŋyaŋma (Goin), sĩ'ngnamã (Goin)	[13,14]
Burundi (Zaïre-Nil peaks region and Western Burundi)	Umubwirrwa, umubwiga, umujisharugi (Kirundi)	(a)
Cameroon (northern region)	Tiami (Fulfuldé)	[15]
Central African Republic (Gbaya dialect, Bossangoa)	Marro	[16]
Comores	M'haniba (Grande Comores)	(a)
Democratic Republic of Congo (Itury forest)	Njima (Mbuti pygmies)	[17]
Ethiopia (Omo Zone), (Arsi Zone)	Tania, qacaaculee	[18,19]
Fiji	Pou	[1]
France	Balan des savanes	(a)
Ghana (Dangme West district)	Asre (Adangbe)	[20]
India	Perimklavu, vellapoolam (Malayalam); pithondi	[21,22]
Ivory Cost	Môgôcolo-calaman (Dioula); mokokoana, mokrodoma (Malinké)	[23]
Kenya (Bungoma district), (Kilifi district)	Lubwili (Bukusu); mukwamba (Giriama); kiptarpotich, chepochepkai (Pokot); mkwamba (Swahili); mukuluu (Kamba); lkirebuki (Dorobo) (Suiei)	[24–29]
Madagascar	Kotika (Antakarana); atsikana, fantsikakoholahy, patikakoho, teto, voafotsikotikana (Malagasy)	[30]
Mali (Dogonland) (Niono district)	Jene, surukujè (Bambara); nginnin (Malinké); jene (Minyanka); jeme (Sénoufo); sutèmi, sudèrèmi (Bwa); sumenh (Bobo-fing); segele (Dogon); déné, nkoloningé, baram baram, karam karam (Bambara); kolonidiè (Bamanan); ndjene (Bambara); segedere, ségélé, sèsègèrè, balambalam	[31–35]
Mozambique (Massingir district)	Nsangasi, sangasi (Changana)	[36]
Niger	Fulasco (Hausa), kamal (Peuhl), dagkirto (Béribéri), tsa	[37]
Nigeria	Iranje (Yoruba), tsuwawun karee (Hausa), njisinta (igbo)	[38,39]
Nigeria, Benin, Togo	Iranje (Yoruba people)	(a)
Philippines	Anislag or anislog, (Bikol, Cebu Bisaya, Samar-Leyte Bisaya, Manobo, Mandaya); anislang, hamislag (Bikol); katamangan, malangau (Manobo); tras (Magindanao)	[1]
Samoa	Poumuli	[1]
Senegal (Saloum Islands)	Sambelgorel, tembelforel (Peul); baram baram, dene, balamanten, tene (Bambara); mbarambaram, faragfarag, maymayin (Sérère); keng (Wolof); fusabel fu nene, e buker, ba herer (Diola); bouroum baran (Socé); tembel gorel (Peul, Toucouleur)	[33,40,41]
Solomon Islands	Mamufu'a or Mamufua (Kwara'ae), mewana (Bougainville Island)	[1]
Somalia	Xararaay	[42]

Table 2. *Cont.*

Country (Region or Province)	Vernacular Names (Language)	References
South Africa (Northern Maputaland), (Vhavenda), (Limpopo province), (Mpumalanga province), (Limpopo province)	Ihlalanyosi (Zulu); mutangauma (Venda); witbessiesbos (Afr.); mutangahuma (Tshivenda); mpfalambati (Tsonga); muhlakaume (Sotho); motlhalabu, motlhakawume, mohlakauma	[43–46]
Tanzania, Kenya, Mozambique *(Swahili)*	Mkwamba, mkwamba maji, mteja	[47]
Tanzania (Katoro Ward, Bukoba District), (Lushoto and Korogwe districts), (Handeni district), (Tanga district), (Kimboza forest reserve in Morogoro), (Muleba district)	Mkwambikwamb, lukwambikwambi (Kibunga); omubwera, omutoruka, muumbiti, muhumba, mkwamba, mtulavuha, msokote, mkalananga, mturuka, eruati, mkwambe (Ndengereko, Swahili, Zaramo)	[48–52]
Togo (Maritime region)	Kébantchalé, kébantialé, kégbantilé, akassélem, hesré (Mina, Ewé); tchakatchaka (Tem, Kabiyé, Fè, Adélé); tchacatchaca (Tem); hesre	[53]
Uganda (Budiope county), (Sango bay area), (Apac district), (Mabira Central Forest Reserve), (Langi language, Erute county, Lira district)	Lukandwa, olukandwa, iakara, ilakara, omukarara (Runyaruguru); omukalali (Rukonjo); lukandwa (Luganda)	[54–60]
Vanuatu	Mamau (Butu), nemameiu (Hiu)	[1]
Wallis and Futuna	Poutea	[1]
Zimbabwe (Harare and Nhema area, south-central region)	Muchagawuwe (Shona), umhakawuwe (Ndebele)	[61,62]
Zambia (Lusaka)	Lukuswaula	[1]

[a] http://www.ethnopharmacologia.org/recherche-dans-prelude/?plant_id=5358 (accessed on 15 December 2023).

The ripened fruit of *F. virosa* are edible small white berries that are about 5 mm in diameter. At maturity, they are claimed to be juicy and sweet, though with a slightly bitter flavor. They are eaten by people, animals and birds when ripe. They are consumed fresh or boiled to make sauces or cooked together with the powder of cultivated crops to make porridge by the Kara and Kwego people in Ethiopia [18]. The pulp of the fruit is used to cure itching by rubbing on the skin [63]. The plant is recognized for its important nutritional properties with high palatability, and therefore, it is largely used as cattle fodder by breeders in Benin [64]. It has also been used as an antivenin medication for the treatment of snakebites, notably in Uganda [21,63,65].

A large diversity of bioactive natural products was identified from *F. virosa* and different types of plant extracts have revealed marked pharmacological activities. The present analysis offers an overview of the properties of *F. virosa* and its phytoconstituents. The traditional uses of the plant were analyzed based on an extensive review of the published information on *Flueggea virosa* and its different synonyms, notably *Securinega virosa*, which is also a commonly used name (Table 3). The objective was to highlight the benefits of the plant and to promote its use and new research activities. A comprehensive literature search was performed up to November 2023 using multiple databases and keywords. This review offers an exhaustive analysis of the scientific literature on *F. virosa*, including publications, reports and patents (mainly in the English language). This topic has not been addressed before and the phytochemical richness of the plant, notably the presence of unusual oligomeric alkaloids, piqued my interest.

Table 3. Synonyms for *Flueggea virosa* (Roxb. ex Willd.) Royle (1836) [1].

- *Acidoton virosus* Ktze. (1891)
- *Flueggea abyssinica* (A. Rich.) Baill. (1858)
- *Flueggea angulata* Baill. (1860)
- *Flueggea microcarpa* Blume (1825)
- *Flueggea obovata* (Willd.) Wall. Ex Fern.-V. (1880)
- *Phyllanthus angulatus* Schumach. & Thonn. (1827)
- *Phyllanthus virosus* Roxb. ex Willd. (1805)
- *Securinega abyssinica* A. Rich. (1850)
- *Securinega microcarpa* (Blume) Müll.Arg. (1866)
- *Securinega obovata* (Willd.) Müll.Arg. (1866)
- *Securinega virosa* (Roxb. ex Willd.) Baill. (1866)
- *Xylophylla obovata* Willd. (1809)

[1] According to https://www.worldfloraonline.org/ (accessed on 15 December 2023).

2. Pharmacological Effects of *F. virosa* Extracts

Extracts prepared from the aerial parts of the plant or the roots have been largely used in traditional medicine to treat human diseases. The main properties of these extracts are discussed in turn (Figure 2).

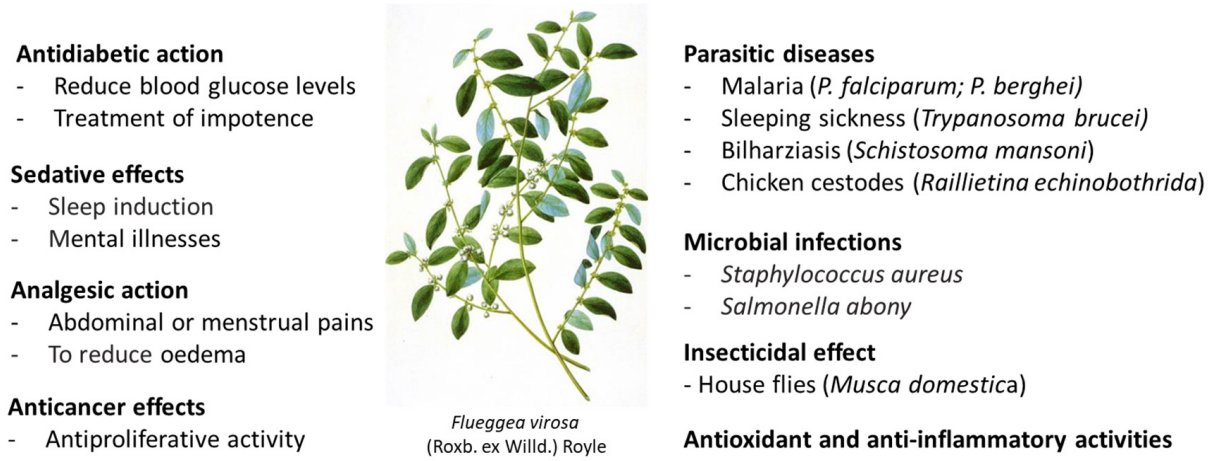

Figure 2. Pharmacological properties reported with extracts of *F. virosa*.

2.1. Antiparasitic Activities

The plant is used against malaria in Kenyan folk medicine [66] and in Ghana [20] and other African countries to treat parasitic diseases. A methanol extract made from fresh leaves of *F. virosa* (collected in Comoros) was shown to inhibit the growth of the malaria parasite *Plasmodium falciparum* in vitro (IC_{50} = 2.28 and 3.64 μg/mL, with strains D6 and W2, respectively), with no significant effects on control non-infected Vero E6 cells (CC_{50} = 683 μg/mL). In vivo, the same extract was found to reduce the growth of *Plasmodium berghei* in infected mice by more than 70% when administered at 100 mg/kg/day. The effect was modest but noticeable with a mean survival time of 11 days versus 8 days for the vehicle-treated control group. No apparent sign of toxicity was observed [24–26]. Moderate antimalaria activity was confirmed using another chloroquine-resistant strain of *P. falciparum*, namely, strain K1 (IC_{50} = 7.6 μg/mL) [13]. A marked antiplasmodial activity was obtained with a methanol/water leaf extract and with a root decoction (IC_{50} = 3 μg/mL) [67]. But the best evidence of activity comes from a study that employed an ethyl acetate fraction of *F. virosa* leaves, which revealed dose-dependent activity in *P. berghei*-infected mice, with a nearly complete (86%) suppression of the animal parasitemia and a mean survival time of 17.2 days versus 10.8 days for the control animals [68]. The antimalaria activity was attributed to the presence of the polyphenol bergenin (see below). The plant is not a universal treatment because a similar methanolic extract was found to be inactive against the chloroquine-sensitive strain of *P. falciparum* PoW (IC_{50} > 50 μg/mL) [69]. Nevertheless, *F. virosa* is recognized among major African medicinal plants to treat malaria [70].

The alcoholic plant extract may be used also to combat other parasites. A leaf extract of *F. virosa* (collected in Mizoram, India) was found to be active against the intestinal cestode parasite *Raillietina echinobothrida*, which infects domestic fowl. The extract significantly reduced the alkaline phosphatase activity and induced protein catabolism in treated parasites [71]. The anthelmintic activity has been associated with the induction of significant destruction of the parasite tegument with intense vacuolization and swellings of the basal lamina leading to deformities in the cell organelles [72]. Antitrypanosomal activity was also reported with a petroleum ether extract of *F. virosa*, which was found to reduce the growth of *Trypanosoma brucei rhodesiense* (IC_{50} = 0.5 μg/mL), whereas the maximum tolerated concentration was about 20-fold higher (MTC = 9 μg/mL) [73]. Here, again, the antitrypanosomal activity of the extracts can be attributed to the presence of bergenin, which was shown to inhibit the growth of the bloodstream form of *Trypanosoma brucei* (IC_{50} = 1.0 μM) [74]. This natural product is a model compound for designing semi-synthetic products that are active against *T. brucei* [75]. The marked activity observed with the plant extract explains why traditional healers in Uganda use a powder from pounded roots of *F. virosa* (one spoonful orally) to treat sleeping sickness [73].

The root extract of *F. virosa* may be used to combat bilharziasis (schistosomiasis). A traditional recipe used in Somalia recommended the use of fresh roots, crushed and boiled with water to prepare a drinkable solution active against the parasite [42]. But no information about the efficacy of the preparation is available. Similarly, the use of a root decoction to treat urinary schistosomiasis is cited in a review on plants used to treat schistosomiasis in Niono District in Mali, but without further details [31]. Experimental data to support the antischistosomal activity are needed because an ancient study only revealed a minor effect of a leaf extract of *F. virosa* on cercariae and miracidia of *Schistosoma mansoni* [76].

2.2. Antimicrobial Effects

The traditional use of *F. virosa* for the treatment of dermal infections and wounds in Ghana has motivated studies aimed at characterizing the potential activity of various polar/apolar extracts of the plant against several organisms. Among the different medicinal plants tested, *F. virosa* was the most active, notably the chloroform extract derived for the root bark, which was found to be active against 13 microorganisms tested, but with a variable degree of activity. The $CHCl_3$ extract was most potent against the pathogenic Gram-negative species *Salmonella abony* (MIC = 15.6 µg/mL) and mildly active against *Staphylococcus aureus* (MIC = 125 µg/mL). Interestingly, the extract was found to potentiate the activity of the antibiotic norfloxacin against a norfloxacin-resistant strain of *S. aureus* possessing the efflux pump NorA. Antimicrobial activities against other pathogens, such as *Bacillus subtilis*, *Micrococcus flavus* and *Pseudomonas aeruginosa* were also observed (17, 19 and 12 mm of growth inhibition when using an agar well diffusion technique) [77]. A recent study underlined the activity of *F. virosa* leaf extracts against *methicillin-resistant Staphylococcus aureus* (MRSA) [78], in agreement with other antimicrobial studies [79,80].

2.3. Antiepilepsy and Antipsychotic Activities

The testing of different Malian plants used traditionally to treat epilepsy and convulsions has revealed a marked activity with a leaf extract of *F. virosa* (with a plant collected in Bougouni District, Southern Mali). The extract inhibited the spontaneous discharge (SED) in a mouse cortical wedge preparation (IC_{50} = 0.2 mg/mL) and was efficient in the [^{3}H]-flumazenil-binding assay (IC_{50} = 0.45 mg/mL), suggesting the presence of GABAergic compounds. The extract showed no effect during anticonvulsive testing in a model of pentylenetetrazol-induced seizure in mice [81]. A similar methanolic extract, which was also prepared from leaves of *F. virosa*, was shown to decrease aporphine-induced stereotypic climbing behavior, reduce swim-induced grooming in mice and increase the mean duration of ketamine-induced sleep in a murine model at a dose of 50 mg/kg [82,83]. The extract facilitated sleep induction, as was also shown in another study with a model of diazepam-induced sleep. In this case, an extract at 100 mg/kg was shown to prolong the duration of diazepam-induced sleep without affecting the exploratory behavior or the motor coordination of mice [84]. These observations using experimental models are consistent with the traditional use of plant extract as a sedative in children and for mental illnesses.

Sedative effects were also observed when using root bark extracts of *F. virosa*, notably with a butanol extract that contained tannins, saponins, alkaloids, flavonoids and cardiac glycosides, as with the methanol extract. A butanol fraction administered to mice (75 mg/kg) was found to reduce the mean onset of sleep and to double the mean duration of sleep. The sedative effects were clearly established [38,85]. A bark extract also displayed an antipsychotic activity, reducing swim-induced grooming activity in mice and the mean climbing score [86]. This latter study was performed using a residual aqueous fraction of methanol root bark extract but it gave results comparable with those obtained with the methanolic leaf extract, suggesting the implication of the same bioactive principles [83]. One of the active principles was clearly identified: the polyphenolic substance bergenin, which is present in the plant roots and aerial parts and was shown to possess a sleep-inducing property. This compound may, at least in part, be responsible for the seda-

tive potential of the plant extracts [87]. Bergenin is found in many plants and is known to display antioxidant and antianxiety activities [88,89].

2.4. Antidiabetic Effects

One of the traditional usages of *F. virosa* is the treatment of diabetes-related impotence [54]. The chronic hyperglycemia that characterizes type 2 diabetes can lead to alteration of the vascular endothelium and associated tissue damage, notably a marked erectile dysfunction, which is considered the most important sexual dysfunction in men with diabetes mellitus [90]. Traditional healers in the Tanga region of Tanzania (northeastern part) use aqueous extracts of *F. virosa* to treat impotence and as an aphrodisiac [91]. Experimental data show that the oral administration of an aqueous extract prepared from dried roots of *F. virosa* reduces the blood glucose level in rabbit, but only during hyperglycemia. The extract has no effect once blood glucose has reached fasting levels. A dose-dependent (0.1–1.0 g/kg body weight) reduction in the area under the oral glucose tolerance curve was observed and no major toxicity was noted [47]. Antidiabetic effects have also been reported with a leaf extract of *F. virosa* administered intraperitoneally to diabetic rats. In this case, the extract reduced blood glucose levels after 4–24 h of administration, with an efficacy relatively close to that of the reference product insulin (at 24 h, the glucose levels were 328.2, 165.4 and 137.0 mg/dL in the groups treated with saline buffer (control), 100 mg/kg *F. virosa* leaf extract and 6 i.u./kg insulin, respectively) [92]. Thus, the extract clearly presented an insulin-like effect. Recently, a similar observation was made with a hydro-ethanolic plant extract (200 mg/kg) administered to streptozotocin-induced diabetic rats. The plant treatment reduced hyperglycemia and the progression of diabetic nephropathy [93]. *F. virosa* is regularly cited as a plant used traditionally in Africa to treat diabetes mellitus [91,94,95], but the natural products at the origin of the antidiabetic effects have not been identified at all. This aspect of the plant warrants further investigation. Among the antidiabetic compounds, it is worth mentioning the trimeric alkaloid fluevirosine A (see below). Its use in the preparation of blood-sugar-reducing medicine was patented in China [96].

2.5. Antidiabetic Effects

In relation to diabetes, we can also refer to the use of *F. virosa* extracts for the treatment of diabetes-associated pain. In Mali, decoctions made from the root, root bark or leaves are taken orally to relieve painful conditions, including stomach ache, menstrual pain and pain due to diabetes [32]. A methanol root bark extract of *F. virosa* was shown to display analgesic effects in animal models. The extract inhibited acetic acid-induced abdominal constrictions and attenuated formalin-induced neurogenic pain. The extract efficiently reduced abdominal writhing in mice in a dose-dependent manner. Remarkably, the inhibition of abdominal constriction with the plant extract at 25 mg/kg was greater than that of the standard non-steroidal analgesic piroxicam. Moreover, in a model of carrageenan-induced paw edema in rats, the methanol root bark extract was shown to efficiently reduce the edema diameter, with an efficacy close to that of the reference product ketoprofen [97]. In these in vivo tests, the most active doses were 25–100 mg/kg, which was largely inferior to the intraperitoneal median lethal dose (LD_{50} = 1.26 g/kg), suggesting that the extract is relatively safe at the analgesic doses [98]. Analgesic effects were also observed with an aqueous root extract (100–400 mg/kg) in a model of thermally induced pain in rats [99]. The aqueous root extract was apparently less efficient than the methanol root extract. Experiments were also performed with aqueous extracts prepared from the leaves and stems of *F. virosa* using a model of acetic acid-induced pain in mice. Interestingly, the stem extract displayed a marked analgesic effect (65% pain inhibition) coupled with a significant anti-inflammatory activity (59% inhibition of carrageenan-induced inflammation in mice) [100]. Collectively, these different studies support the traditional use of *F. virosa* to manage pain associated with different diseases and conditions, such as diabetes, but also benign prostatic hyperplasia (BPH).

2.6. Anticancer Effects

Decoctions from the roots of *F. virosa* are traditionally used to treat cancer patients. Notably, the Embu and Mbeere peoples in Kenya use root decoctions to treat prostate and breast cancers and kidney problems [27,101,102]. An antiproliferative action was also observed with a methanol extract and the human cancer cell lines RD (rhabdomysarcoma) and Hep-2C (laryngeal carcinoma) (IC_{50} = 11.3 and 7.2 µg/mL, respectively) [103]. The plant contains numerous alkaloids that can inhibit the proliferation of cancer cells. These different products are discussed below, notably a series of antiproliferative indolizidine alkaloids. There are also anticancer studies with the plant extracts, notably a study revealing the capacity of a methanolic leaf extract to block the proliferation of MCF7 breast cancer cells and NCI-H460 lung cancer cells (GI_{50} = 42.2 and 78.3 µg/mL, respectively). The root bark extract was a little less active than the leaf extract, and the chloroform fraction was more active than the aqueous fraction (essentially inactive) [104]. Interesting data have also been reported for a root bark extract, which was found to inhibit the proliferation of U-1242 glioblastoma multiforme tumor cells. Here, again, the chloroform fraction was the most active, and the crude methanol root bark extract was shown to modulate the epidermal growth factor receptor (EGFR) pathway [105].

2.7. Antioxidant Effects

Unsurprisingly, several studies referred to the antioxidant activity of *F. virosa* extracts, which is a property commonly observed with plant extracts containing flavonoids and phenolic compounds [106]. The best activity was obtained with ethanolic leaf extracts, whereas hexane extracts were much less active [107]. The leaf methanol extract presented higher antioxidant effects than the stem bark methanol extract [108,109]. The leaf extract was found to be as efficient as the reference product ascorbic acid (IC_{50} = 25 µg/mL in a DPPH assay) [88]. An extract made from the aerial parts of *F. virosa* revealed an antioxidant action that was a little inferior to that of ascorbic acid (IC_{50} = 0.01 versus 0.008 mg/mL, respectively), coupled with antifungal and antiproliferation effects [103]. Diverse antioxidant products were isolated from the leaves, such as bergenin, but also kaempferol 3-*O*-(4-galloyl)-β-D-glucopyranoside, 11-*O*-caffeoylbergenin and glucogallin acting as hydroxyl radical scavengers [77,110]. Root extracts also displayed a marked antioxidant profile [79]. The main component bergenin contributes significantly to the antioxidant effects. This phenolic compound alleviates hydrogen peroxide-induced oxidative stress in cells [111,112]. The antioxidant properties of *F. virosa* have been amply documented. Among 47 plant species (27 families) used in traditional medicine in Burkina Faso, a total extract of *F. virosa* revealed the most important antioxidant capacity [113].

2.8. Other Activities

Occasionally, other properties were observed when using extracts of *F. virosa*, such as antiarrhythmic effects attributed to bergenin [114]. The capacity of bergenin to protect from myocardial ischemia–reperfusion injury is well documented [115]. Recently, an ethanolic extract made from the aerial parts of *F. virosa* has demonstrated antisickle cell activity via a capacity to normalize the shape of the circulating abnormal erythrocytes, which is the so-called antifalcemic or antisickling activity [116]. The same type of activity was demonstrated previously with an aqueous methanolic leave extract, which inhibited sodium metabisulphite-induced sickling of hemoglobin sickle-shaped (Hbss) red blood cells in a concentration-dependent manner [117]. The antisickling is attributed to the presence of phenolic compounds capable of modulating the inflammatory response and reducing the vasocclusive crisis, but also to amino acids and flavonoids targeting Hbss polymerization and reducing endothelial dysfunctions [116].

There are not many studies that investigated the activity of *F. virosa* extracts against pathogenic fungi. Minor activities against *Candida albicans* [66] and the dermatophyte *Trichophyton interdigitale* (MIC = 125 µg/mL) [77] were noted. Similarly, modest activity was observed with a root bark extract tested against *Candida albicans*, *C. glabrata* and *C. tropi-*

calis [118]. The plant extracts are not very active against fungi and different alkaloids from the plant tested, as antifungal agents revealed little or no activity. For example, the alkaloid virosecurinine was found to be inactive against various fungi, such as *Aspergillus niger*, *Penicillium viridicatum* and *Fusarium monoliforme* [119].

Other pharmacological activities have occasionally been reported, such as an antidiarrheal activity with *F. virosa* methanolic extract [120,121] or the treatment of skin rashes and HIV infection [122]. The plant contains monomeric and dimeric alkaloids acting as inhibitors of HIV replication, such as virosinine A and flueggenine D (see below) [6,123,124]. A leaf powder of *F. virosa* can also be used as an insecticidal agent, for example, to control the development of the house fly *Musca domestica* and the transmission of diseases to humans [125].

3. Phytochemical Analyses of *F. virosa* Extracts

Over the past 30 years, the chemical constituents of the plant have been investigated using different geographic sources and different parts of the plant. Three main product categories can be defined: (i) polyphenols, which are typified by the lead product bergenin and flavonoids, (ii) multiple terpenoids and (iii) alkaloids, in addition to a few other products (saponins, polyketides, steroids, cyano glucosides, etc.). More than 80 natural products were identified belonging to the three main categories, which are discussed in turn below.

3.1. Polyphenols and Flavonoids

The major active component of *F. virosa* is certainly the polyphenolic isocoumarin bergenin, which is a *C*-glycoside of 4-*O*-methyl gallic acid and can be mainly found in the aerial parts of the plant, but also the roots, notably the root bark [87] (Figure 3a). Bergenin was discovered more than 140 years ago and is distributed in more than 11 plant species. This common compound displays a wide range of pharmacological properties (antiparasitic; antimicrobial; antinociceptive; antiarthritic; antidiabetic; antiarrhythmic; anticancer; and cardio-, hepato- and neuroprotective activities) [126,127]. It is likely at the origin of many of the effects observed with *F. virosa* extracts, notably the antioxidant, antianxiety, antiarrhythmic [114] and trypanocidal activities [74].

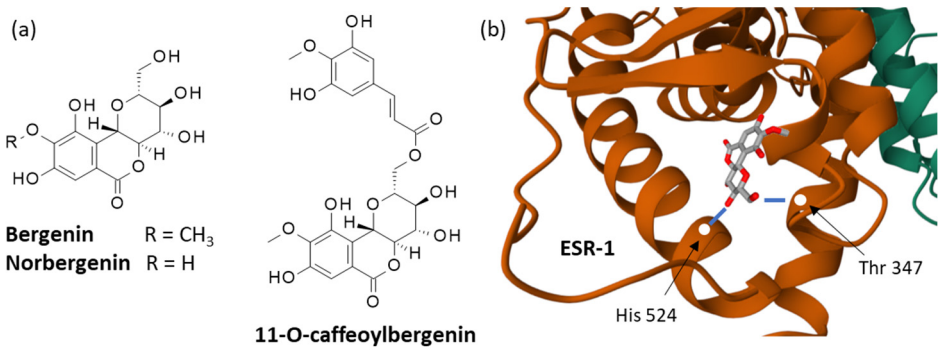

Figure 3. (**a**) Structures of bergenin, norbergenin and 11-O-caffeoylbergenin isolated from the leaves of *F. virosa*. (**b**) Molecular model of bergenin bound to ESR-1 (estrogen receptor 1), with two major hydrogen bonds between the drug and residues Thr347 and His524 of ESR-1 [128].

Its mechanism of action is multifactorial. A recent molecular modeling study postulated a direct interaction of bergenin with the ligand-binding domain of the estrogen receptor 1 (ESR-1) [128]. The hydroxyl groups on the C ring of the drug engage in contacts with the residues His-524 and Thr-347 of ESR-1 (Figure 3b). But other protein targets are implicated in the mechanism of action. Previous studies also suggested the binding of bergenin to the proteins NLRP3 (NOD-like receptor family-pyrin domain containing 3) inflammasome [129], antiapoptotic protein B-Cell Lymphoma 2 (Bcl-2) [130], enzyme galectin-3 [131] and several other proteins [132–135].

Derivatives were also found, such as norbergenin, 11-*O*-acetyl bergenin and 11-*O*-caffeoylbergenin isolated from the leaves of *F. virosa*, together with flavonoid glycosides (e.g., kaempferol 3-*O*-(4-galloyl)-β-D-glucopyranoside) and phenolic derivatives [110,136,137]. Among these products, the demethoxylated form of bergenin, which is known as norbergenin (Figure 3a), is a potent inhibitor of oxidative stress, acting as an efficient scavenger for oxygen-based radicals [138] and a potent anti-inflammatory agent [139].

Analytical methods were implemented to quantify the contents of products in the plant [140]. It was determined that the aerial parts of *F. virosa* contain 15.2% (*w*/*w*) of bergenin [141,142]. A methanolic extraction process can be applied to extract the product from the leaves [114]. This abundant polyphenolic compound is used as a template for the design of novel semi-synthetic antiparasitic drugs [75]. The naturally occurring derivative 11-*O*-caffeoylbergenin (Figure 3a) displays marked antioxidant and antiarthritic activities [143,144]. Bergenin itself is an anticancer agent that acts as a suppressor of glycolysis and, therefore, is useful to overcome chemo- and radio-resistance [145,146]. Its mechanism of action notably implicates the targeting of the antiapoptotic protein Mcl-1 (Myeloid leukemia 1), which is frequently overexpressed in human malignancies [147]. Bergenin presents a limited bioavailability, but there are options to overcome this limitation, notably through the design of semisynthetic derivatives and the use of micro-/nano-delivery systems for a controlled release of the product [133,148,149]. The abundance of bergenin in *F. virosa* is a major element of the bioactivity of the plant. Nevertheless, the pharmacological use of this compound (or the plant) must be limited because, at high doses, the compound can impair the physiology of different organs (liver, kidneys, intestine) and some of its metabolites are suspected to be carcinogenic [150].

Other polyphenolic compounds can be found in *F. virosa*, notably the common dietary flavonol rutin [151]; the ellagitannins corilagin, acalyphidin M and geraniin; the gallic acid derivative glucogallin [109]; and (2S,3R)-4E-dehydrochebulic acid trimethyl ester [152]. These natural products, which are often present in natural medicines, are potent antioxidant compounds [153]. Corilagin is well recognized for its anticancer effects [154,155] and its anti-inflammatory effects [153].

3.2. Terpenoids

A recent study characterized a series of polyoxygenated terpenoids designated podovirosanes A–F from the roots of *F. virosa* (Figure 4). They are tricyclic molecules with a mild anti-inflammatory activity, at least for some of them, but their bioactivity remains little known at present [156]. They bear a structural analogy with flueggenoids A–E isolated from the twigs and leaves of *F. virosa* (Figure 4). In this series, only flueggenoid C revealed a modest inhibitory activity against hepatitis C virus (HCV) infection (IC_{50} = 23.3 μM) and no cytotoxicity against human hepatocellular carcinoma Huh7.5 cells (IC_{50} = 92.8 μM). The other compounds were inactive. Several 13-methyl-*ent*-podocarpanes were co-isolated during the process to obtain the flueggenoids, but these compounds also revealed a very modest anti-HCV activity [137]. Another series of terpenoids was isolated from the roots of *F. virosa* and evaluated for their potential anti-HCV activity. The series of 18 compounds included many *ent*-podocarpanes, which were more or less rearranged. Two compounds, including compounds **4** and **8** (Figure 4), exhibited a modest inhibitory activity against HCV infection (IC_{50} = 14.4 and 17.8 μM, respectively) [157]. The tricyclic podocarpatriene **8** warrants further investigations as an antinociceptive agent because it bears a structural analogy with the podocarpatrienone that is active in models of hyperalgesia [158]. Another compound, namely, 9(10− > 20)-*abeo*-*ent*-podocarpane, was found in a twigs and leaves extract and characterized as an inhibitor of HCV infection in Huh7.5.1 cell cultures (EC_{50} = 27.4 μM). Better activity was obtained with the derivative **4** (Figure 4), with an EC_{50} of 7.7 μM and a satisfactory selectivity index (SI = 9.2) [152]. Podocarpane-type diterpenoids are not extremely frequent in nature [159] and their bioactivities are generally little known.

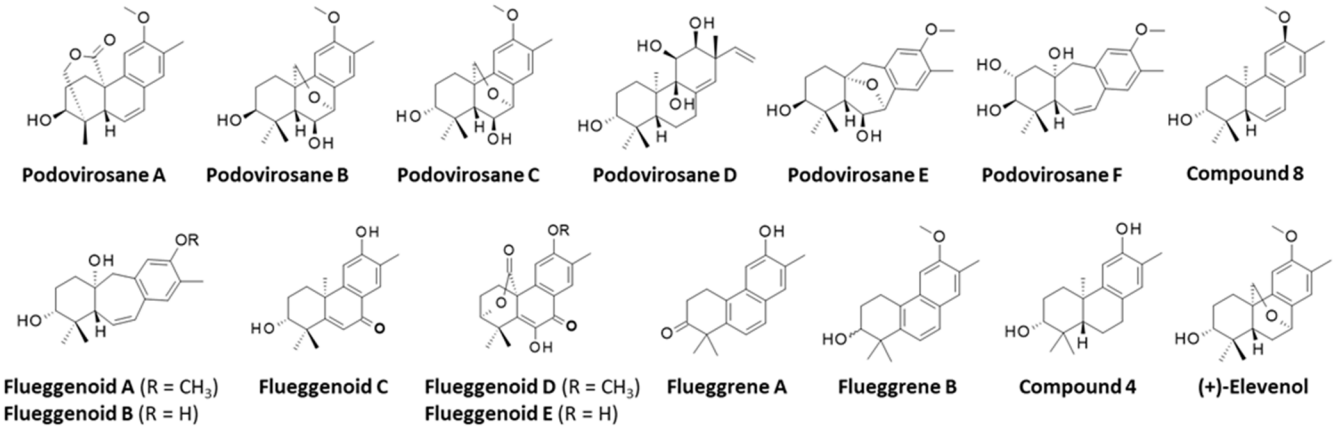

Figure 4. Podocarpane-type diterpenoids found in *F. virosa*. Compounds **4** and **8** correspond to 3β,12-dihydroxy-13-methylpodocarpa-6,8,11,13-tetraene [152] and 3α-hydroxy-12-methoxy-13-methyl-ent-podocarpa-8,11,13-triene [157], respectively.

In the same group of podocarpane derivatives, flueggrenes A and B (Figure 4) are two trinorditerpenes that were also isolated from the roots of *F. virosa*. They display a weak anti-HCV infection activity (IC_{50} = 13.0 and 26.3 μM, respectively) and they are both able to inhibit elastase release by human neutrophils in response to cytochalasin B (IC_{50} = 4.3 and 9.6 μM, respectively) [160]. In the same vein, the authors also described a series of dinorditerpenes found in *F. virosa* roots, including a few potent compounds. An interesting molecule is the podocarpatriene 11 (7α,20-epoxy-3α-hydroxy-12-methoxy-13-methyl-ent-podocarp-8,11,13-triene) with an intramolecular ether linkage. This compound was found to reduce HCV infection (IC_{50} = 6.6 μM) while being non-cytotoxic to Huh7.5 cancer cells (IC_{50} > 400 μM) [161]. Its high therapeutic index (TI = 56) encouraged further studies, as well as the total synthesis of the compound renamed (+)-elevenol (Figure 4) and that of a close analog named (+)-przewalskin [162]. There is now a convenient synthetic procedure to access these antiviral compounds. In fact, podovirosane B is a 6-hydroxy derivative of (+)-elevenol.

Diverse triterpenoids were isolated from the leaves and twigs of *F. virosa* and evaluated as anticancer agents. Friedelin, heptanolide, epifriedelanol, stigmasterol and betulinic acid were identified and the later pentacyclic triterpene was found to be the most active against cancer cell proliferation in vitro [163]. Nothing is surprising here, as betulinic acid is well known to display marked anticancer activities [164,165]. Other common triterpenoids were identified from extracts of the stem bark and leaves of the plant, such as the saponins oleanic acid (C15) and ursolic acid (C16), both of which are very abundant in the stem bark (88–94 mg/g), but also asiatic acid, maslinic acid, corosolic acid and other minor terpenoids (1–7 mg/g) [109,166]. Ursolic acid is a potent anti-inflammatory and antioxidant compound that is of interest in combating multiple diseases, notably urogenital cancer [167,168].

3.3. Alkaloids

Flueggea (or *Securinega*) alkaloids have been studied for more than half a century. It started in the mid-1950s with the isolation of securinine from *Securinega suffruticosa* (Pall.) Rehd. in Russia [169], followed by the discovery of virosecurinine from *F. virosa* in 1963 [170] (Figure 5). Over the past sixty years, many alkaloids have been identified from all parts of plants collected in different territories. The plant generates a multitude of alkaloids, including oligomers biosynthesized from (-)-norsecurinine as a monomeric precursor. Dimers, trimers, tetramers and pentamers were identified, such as flueggenines C and D (dimers), fluevirosine D (trimer), fluevirosinine A (tetramer) and fluevirosinines G–J (pentamers), all from *F. virosa*. Many alkaloid-related studies were performed with

the species *S. suffruticosa*, with a wide range of structures [171–173]. Here, we focus on selected alkaloids from *F. virosa* only.

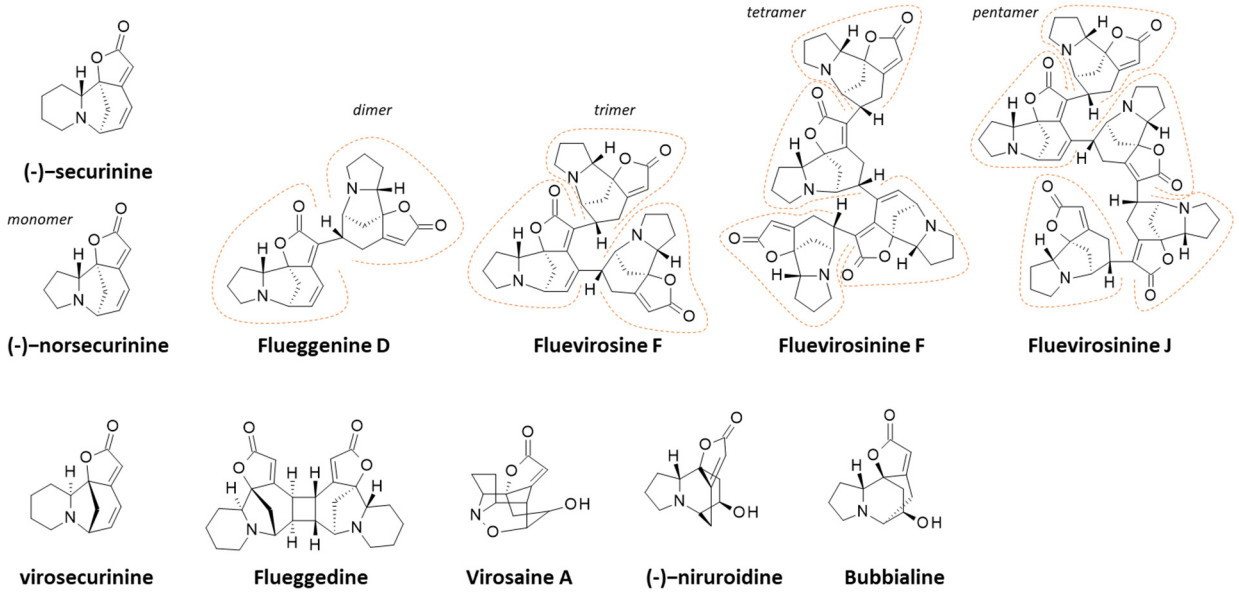

Figure 5. Monomeric and oligomeric alkaloids isolated from *F. virosa*.

Securinine can be considered the leading alkaloid from *F. virosa*; it is also largely present in other *Flueggea* species [174]. Among the diverse pharmacological effects of the compound, the anticancer properties deserve special interest owing to the potency of the compound and its mechanism of action that implicates several signaling pathways, notably the AKT/mTOR/S6K pathway, JAK/STAT pathway and MAPK (MEK/ERK) pathway, leading to mitochondria-mediated apoptosis within cancer cells [175,176]. Different molecular targets were postulated, notably a direct interaction between securinine and tubulin (Kd = 9.7 μM) [177]. Securinine has been largely used as a prototypic scaffold for the design of analogs developed as antitumor agents and/or neuroprotective compounds [178–180].

The structural diversity within the securinine-type family of alkaloids is large, with about 80 natural products identified from *Flueggea* species [172,179]. A specific search for alkaloids identified from *F. virosa* led to the inventory of 64 compounds (Table 4), which were mostly discovered from the aerial parts and occasionally from the roots or the fruit of the plant. There are also a few distinct alkaloids, such as the small molecule hordenine isolated from the roots and likely serving as a biosynthetic precursor for more complex structures [181]. But the vast majority of alkaloids in *F. virosa* belong to the securinine family. There are many monomeric alkaloids, such as bubbialine, virosine A and niruroidine, but also dimeric (flueggines A and B), trimeric (Flueggether D), tetrameric (fluevirosinine D) and even pentameric (fluevirosinines G–J) alkaloids (Figure 5). Oligomerization of plant alkaloids is not extremely frequent, but it is a feature of the *Flueggea* species, notably *F. virosa* [182,183]. A biosynthetic pathway was proposed, starting from (-)-norsecurinine (monomer) and leading to flueggenines C and D (dimers), and then fluevirosine D (trimer) and fluevirosinine A (tetramer) [184] (Figure 5). One must admit that the many product names are a little confusing. It is not easy to navigate the diverse range of alkaloid names and their properties.

Table 4. Alkaloids isolated from *F. virosa* and their properties.

Compounds	Plant Parts Used (Location of Plant Collection)	Studies and Properties	References
Fluevirosinines A–D	Twigs and leaves (Guangxi, China)	Isolation, structural characterization, proposed biosynthetic pathway. Dimers, trimer, tetramer.	[182]
Fluevirosinines B–J	Twigs and leaves (Guangxi, China)	Isolation, structural characterization, proposed biosynthetic pathway. Inhibitory effect of fluevirosinine B on HIV-1 infected MT4 cells (EC_{50} = 14.1 μM), without cytotoxicity. Tetramers and pentamers.	[124]
Fluevirosines A–C	Twigs and leaves (China)	Isolation, structural characterization, biosynthetic pathway. No antiproliferative activity, but a weak inhibition (35% at 20 μM) of the splicing activity of XBP1 mRNA.	[184]
Fluevirosine D	Twigs and leaves (Guangxi, China)		[182]
Fluevirines A–D	Twigs and leaves (China)	Isolation, structural characterization. Activity against *Staphylococcus aureus*. Fluevirine A showed activity against (MIC = 15.3 μg/mL).	[185]
Fluevirines E and F	Twigs and leaves (Xishuangbanna, Yunnan, China)	Very modest inhibition of cancer cell proliferation (<40% inhibition with fluevirine F at 40 μM).	[186]
Flueindolines A–C	Ripe fruit (Guangxi, China)	Isolation, structural characterization. Tested for neuroprotective activities on Neuro-2a cells and antivirus effects against the respiratory syncytial virus (RSV), but was found inactive.	[187]
Flueggines A and B	Twigs and leaves (China)	Isolation, structural characterization. Potent inhibition of cancer cell proliferation. Flueggine B strongly inhibited growth of MCF-7 and MDA-MB-231 cells (IC_{50} = 135 and 147 nM, respectively), whereas flueggine B was much less active. Total synthesis of flueggine A.	[188,189]
Flueggenines A and B	Roots (China)	Weak antiproliferative activity of flueggenine A against P388 leukemia cells (IC_{50} = 51.5 μM).	[190]
Flueggenines C and D	Twigs and leaves (Guangxi, China)	Isolation, structural characterization. Flueggenine D inhibited HIV-1 infection of MT4 cells (EC_{50} = 7.8 μM) and was weakly cytotoxic (selectivity index = 12.6).	[123,182]
Flueggenines E–I	Twigs and leaves (Xishuangbanna, Yunnan, China)	Isolation, structural characterization. Mild inhibition of MT4 cell infection by HIV-1 (EC_{50} = 42.6 μM) with flueggenine E. Enantioselective synthesis of flueggenines D and I.	[123,191]
Flueggedine	Twigs and leaves (China)	Isolation, structural characterization, proposed biosynthetic pathway from virosecurinine. No antiproliferative activity.	[183]
Flueggether A Virosinine A	Stems and leaves (China)	Isolation, structural characterization. Mild inhibitory effect on HIV-1-infected MT4 cells (EC_{50} = 120 and 45 μM, respectively) without cytotoxicity.	[6]
Flueggethers B–D	Twigs and leaves (Guangxi, China)	Isolation, structural characterization. Dimers (B–D), trimer (D). Inactive against tyrosine kinases c-Met and FGFR1. Flueggether D showed mild anti-HIV activity (CC_{50} = 43.1 μM) on MT-4 cells and was not cytotoxic (IC_{50} > 100 μM).	[192]
Fluvirosaones A and B	Twigs and leaves (China)	Isolation, structural characterization, biosynthetic pathway. Lipid-lowering effects in 3T3-L1 cells: weaker inhibition of triglyceride cellular accumulation compared with virosecurinine.	[193]
Bubbialine, Bubbialidine	Roots (Hainan, China)	Isolation. Total synthesis of bubbialidine.	[194,195]
Securinine, Norsecurinine	All plant parts	Total synthesis. Crystalline structure.	[196–198]
Securinol A Episecurinol A Secu'amamine E	Twigs and leaves (Guangxi, China)	Isolation, structural characterization. Total synthesis of secu'amamine E (and bubbialine).	[199,200]
Norsecurinine Norsecurinic acid Niruroidine	Roots (Hainan, China)	Isolation, structural characterization. (-)-Norsecurinine was found inactive against cancer cells and several bacteria. Total synthesis.	[194,201]
Norsecurinamines A and B	Fruit (China)	Isolation, structural characterization, proposed biosynthetic pathway from tryptophane.	[202]

Table 4. *Cont.*

Compounds	Plant Parts Used (Location of Plant Collection)	Studies and Properties	References
Epoxynorsecurinine	Bark (Venda, South Africa)	Isolation, structural characterization.	[203]
ent-phyllanthidine ((+)-phyllanthidine)	Aerial parts (Saudi Arabia)	Quantification from a methanolic extract (biomarker).	[149]
Virosecurinine Viroallosecurinine	Leaves (Taiwan)	Isolation, structural characterization. Cytotoxic activity against cancer cell lines (EC_{50} = 3–8 μM).	[204]
Virosines A and B	Twigs and leaves (Guangdong, China)	Isolation, structural characterization. The two products and their stereoisomers.	[199,205]
Virosaines A and B	Twigs and leaves (China)	Isolation, structural characterization. Inactive against different cancer cell lines. Total synthesis of virosaines A and B.	[189,195,206]

Apart from the largely studied securinine, the pharmacological effects of all other alkaloids in the series were superficially investigated. Usually, one or two isolated tests were performed, and no comparison can be made between the series. Nevertheless, one molecule emerged from our analysis, namely, the dimeric indolizidine compound flueggine B, which revealed potent antiproliferative activities against two breast cancer cell lines (MCF-7 and MDA-MB-231 cells with IC_{50} values of 135 and 147 nM, respectively), whereas the analog flueggine A was more than 400-fold less active (IC_{50} values of 60 and 68 μM, respectively). Flueggine B is considerably more potent than other compounds that were also tested against the same cell lines, such as dimeric indole fluevirines E and F, both of which were almost inactive (41% growth inhibition with fluevirine F at 40 μM) [186] (Figure 6). Another indolizidine alkaloid dimer, namely, flueggedine (Figure 5), showed no activity against the two identical cell lines MCF-7 and MDA-MB-231 [183]. Other related products were isolated from the fruit of the plant, notably the dimers norsecurinamine A and B (Figure 7), but their pharmacological properties are not known at present [202]. The indole alkaloids named flueindolines A–C were also obtained from the ripe fruit of *F. virosa*. Flueindolines A and B are tricyclic indoles, whereas flueindoline C is a spirooxindole derivative; they possibly derive from tryptophane [187] (Figure 7).

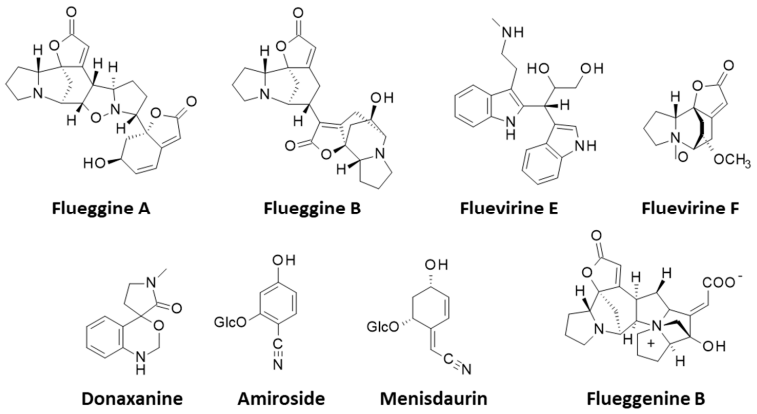

Figure 6. Other alkaloids found in *F. virosa*.

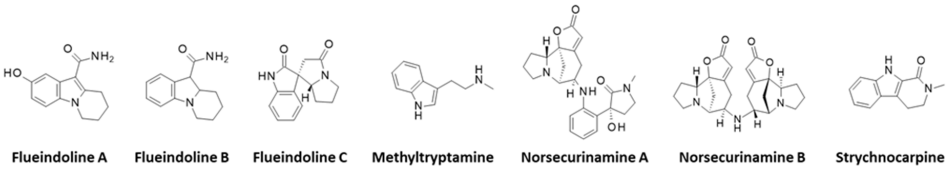

Figure 7. Alkaloids isolated from the fruit of *F. virosa*.

Flueggine B emerged as an atypical compound and perhaps the most interesting in the family (Figure 6). The situation is reminiscent of that previously observed with other dimeric indole alkaloids, such as vinblastine and vincristine derived from the Madagascar periwinkle (*Catharanthus roseus*, formerly *Vinca rosea*). In this case, the dimeric indole alkaloids were much more potent than their monomeric precursor molecules vindoline and catharanthine [207]. It would make sense to evaluate the interaction of flueggine B with tubulin and the effects on the microtubule dynamics. A preliminary docking analysis suggests that flueggine B can form very stable complexes with the α/β-tubulin dimer. The molecular modeling pointed to a binding cavity at the interface of the protein dimer that is suitable to accommodate the monomer securinine or the dimer flueggine B. The calculated empirical energies of interaction (ΔE) were −44.60 and −63.40 kcal/mol for securinine and flueggine B, respectively, and the free energies of hydration (ΔG) were −17.10 and −24.60 kcal/mol, respectively. The binding cavity (297.1 $Å^3$) is large enough to accommodate the dimeric compound, and its interaction with tubulin is stabilized via the formation of two key hydrogen bonds (with residues Leu242 and Lys352), in addition to an array of 16 van der Waals contacts and alkyl/π-alkyl interactions. This is twice the number of H-bonds and contacts observed with securinine under identical conditions (Figure 8). The dimeric compound reveals a prominent capacity to interact with tubulin. We are currently investigating the binding process further. Other alkaloids can be found in *F. virosa*, such as the pyrrolidone donaxanine (Figure 6), and a few indole alkaloids identified from the fruit, such as N-methyltryptamine and strychnocarpine [187]. This latter product is a β-carbolinone alkaloid with a low affinity for the major brain receptors (serotonin, benzodiazepine, tryptamine, opiate and GABA receptors), whereas *N*-methyltryptamine is a mild psychoactive product (Figure 7) [208,209].

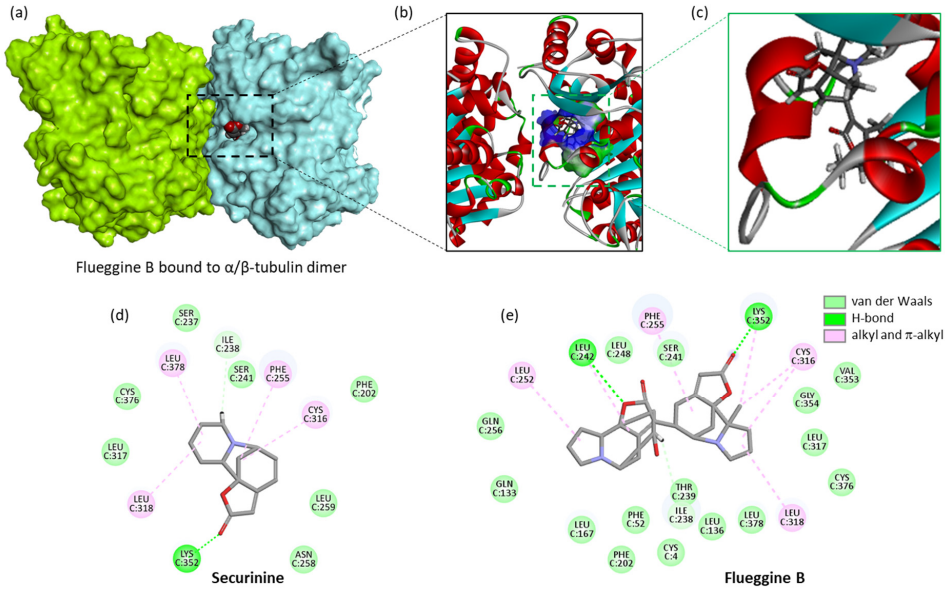

Figure 8. Molecular model of flueggine B (Flg-B) bound to α/β-tubulin dimer (PDB: 5FNV). (**a**) A surface model of α/β-tubulin with bound Flg-B. The α-helices (in red) and β-sheets (in cyan) are shown. (**b**) A close-up view of Flg-B bound to the α/β-tubulin interface with the solvent-accessible surface (SAS) surrounding the drug-binding zone (color code indicated). (**c**) A detailed view of the Flg-B binding site. (**d**,**e**) Binding map contacts for securinine and Flg-B bound to α-tubulin (color code indicated). The docking analysis was performed as recently described using the GOLD docking procedure and the following flexible amino acids around the binding cavity: Phe135, Ser135, Phe169, Cys200, Phe202, Ser241, Leu242, Phe255, Cys316 and Lys 352 [210,211].

3.4. Other Compounds

A few other bioactive molecules were isolated from *F. virosa*, such as the cyano glycoside menisdaurin found in the aerial parts of the plant [139,140] and its analog amiroside [212] (Figure 6). Menisdaurin displays anti-inflammatory properties and possibly functions as an inhibitor of cyclooxygenase-2 [213,214]. Recently, two polyketides were identified from the roots of the plant, namely, (R)-8-methoxymellein and (3R)-5-hydroxy-8-*O*-methylmellein, but the authors suspect that they originated from root symbiotic fungi [156]. Other compounds could be cited, including a few steroids and fatty acids [215].

4. Discussion and Perspectives

The traditional use of the plant *F. virosa* is widespread, notably in Africa, where it is a common folk medicine used to treat many pathologies, such as parasitic infections, inflammatory diseases and diabetes. Decoctions from the plant leaves and twigs are largely used and the fruit are consumed locally. It is a prominent medicinal and nutritional plant. The phytochemical interest of *F. virosa* resides in its large number of bioactive molecules, with two abundant and major products: the polyphenol bergenin and the alkaloid securinine. This latter compound is the leader of the so-called *Securinega* alkaloid family, which includes more than 80 products, with about 65 identified in *F. virosa*. A major phytochemical peculiarity of *F. virosa* is the generation of alkaloid oligomers, with the production of large structures (up to tetra and pentamers) rarely seen in other plants. Alkaloid dimers are relatively frequent (notably among Vinca alkaloids, for example), but tetra and pentamers are much rarer. A few trimeric indole alkaloids have been reported [216–218], but higher-order structures are extremely rare. For example, a tetramer and hexamer of the alkaloid terguride were isolated, but the oligomerization is limited and strongly reduces the high affinity of terguride for 5-HT2A receptors [219,220]. In the case of *F. virosa*, the oligomerization of securinine leads to multiple series of compounds, such as flueggenines, fluevirosinines and flueggedines. The dimers are particularly interesting compounds endowed with anticancer activities. The pentamers are unique. The compounds fluevirosinines G–J represent C-60 macro-structures (fluevirosinine G = $C_{60}H_{65}N_5O_{10}$), which are rarely observed. *F. virosa* is a model plant to study alkaloid oligomerization, the corresponding biosynthetic pathways and the pharmacology of macro-alkaloids.

The strong capacity of flueggine B to interact with tubulin looks promising and should encourage the design and synthesis of novel synthetic dimeric derivatives of securinine. Dimeric securinine analogs endowed with neuritogenic and/or antileukemic activities have been reported [221,222]. One of the synthetic dimers, which was designated SN3-L6, was shown to function as an activator of translation and neuronal differentiation in neural progenitor cells [223]. The same compound also potently and selectively inhibited the proliferation of HL-60 leukemia cells, triggering their apoptosis, but with no effects on megakaryocytes and granulocytes. An investigation into the mechanism of action of this dimeric compound pointed out the mitotic kinases Aurora, with an inhibition of the expression phospho-Aurora kinase A and B expression in HL60 cells treated with this SN3-L6 [222]. This is interesting because Aurora kinases play a major role in mitosis and are implicated in tubulin complexes. This is coherent with a possible modulation of tubulin polymerization via tubulin binding. Both securinine and SN3-L6 are mitotic blockers. These experimental data, coupled with our preliminary docking information, encourage us to investigate the binding of all flueggines to tubulin. Flueggines A and B are present in *F. virosa* [188], but there are also 20 related products, including 9 flueggenines (A–I), 10 fluevirosinines (A–J) and flueggedine found in diverse *Flueggea* or *Securinega* species [210]. Their tubulin capacities will be compared using the same in silico approach as was used with flueggine B and other tubulin-binding natural products [43,211]. The identification of tubulin as a potential molecular target for securinine and flueggine B should help to design new molecules using guided structure-binding relationships. This is an area of major drug design interest.

The plant *F. virosa* warrants further investigation, in particular the fruit, which are abundant and edible. The white berries are often consumed by the local population but

they are not largely exploited and apparently not commercialized in any form, despite their nutritional and medicinal value. In South Africa, the Mapulana people (an indigenous community of Ehlanzeni district in Mpumalanga province, South Africa) consume the fruit, locally called ditlhalabu or ditlhakawume [43]. The berries are consumed in other African countries (Ethiopia, Tanzania) and also in India, notably in the area of the Warud tahsil village, Amravati district in Maharashtra, for their sweet taste and nutritional value [22]. In Ghana, the pulp of the fruit is used for healing wounds and anti-itching, as well as an extract ointment prepared from the leaves of the plant [63,224]. With no doubt, this fruit deserves further studies, with a proper evaluation of its nutritional intake and safety profile. A few alkaloids were isolated from the fruit, but at present, there is no specific study of their pharmacological effects. The biochemical and nutritional composition of *F. virosa* fruit shall be investigated.

In conclusion, this study underlined the pharmacological benefits of the plant *F. virosa*, which is largely used in traditional medicine in a large part of the world. This *Flueggea* species is a phytochemical reservoir, with a large number of flavonoids and alkaloids isolated from different parts of the plant. The two emblematic compounds, namely, bergenin and securinine, along with many derivatives and analogs, are at the origin of the various pharmacological activities, notably anti-inflammatory, antioxidant, antiparasitic, antidiabetic, anticancer and analgesic effects. A remarkable feature of *F. virosa* is the presence of norsecurinine oligomers, such as the anticancer dimer flueggine B, which possibly acts as a tubulin binder. The nutritional and pharmacological properties of the plant, notably the white berries consumed locally, shall be investigated further. In today's rapidly changing world, with a major need to provide healthy food to a growing human population, it is important to accentuate access to a potential new source of food. The fruit of *F. virosa* (and other *Flueggea* species) represents an option to consider but within a frame of ecological protection.

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