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Review

Anti-Tumour Activities from Secondary Metabolites and Their Derivatives in Bryophytes: A Brief Review

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Abstract: Bryophytes are a poorly studied group of land plants that have been used in traditional medicine as a multipurpose remedy for centuries. Due to their peculiar morphology and physiology, bryophytes synthesise a multitude of secondary metabolites with a wide range of nutraceutical and pharmaceutical activities. Research has highlighted that secondary metabolites in bryophytes can also act as antitumour agents. Several studies have shown that bryophyte extracts and pure metabolites are cytotoxic against many cancer cell lines. Interestingly, some of these molecules and their derivatives are capable of acting on a specific target in cancer cells. Some macrocyclic(bis)bibenzyls from bryophytes can inhibit P-glycoprotein, reverting multidrug resistant cancer cell phenotypes, induce depolymerization of tubulin, stimulate apoptotic pathways, and inhibit angiogenesis. This brief review aims to collect recent knowledge on secondary metabolites of bryophytes and their derivatives, which have demonstrated an interaction with different molecular processes in cancer cells.

Keywords: bryophytes; anticancer; multidrug resistance; antiangiogenetic; drug discovery; natural products

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1. Bryophytes and Their Antiproliferative Activity

Cancer is one of the leading causes of death worldwide, accounting for 19.3 million new cases and approximately 10 million deaths in 2020 [1]. Although other treatments have been developed for cancer therapy (gene therapy, immunotherapy, etc.), chemotherapy, surgery, and radiotherapy are the most widely used routine treatments.

Chemotherapy is a treatment based on synthetic drugs that are cytotoxic to cancer cells, inducing cell cycle arrest and apoptosis. Plants, due to their extraordinary diversity of secondary metabolites, have been among the first source of chemotherapy drugs. In the early 1950s, the search for anticancer molecules in plants started with the discovery and development of vinca alkaloids, vinblastine, and vincristine, as well as the isolation of cytotoxic podophyllotoxins [2,3]. From that time onwards, several chemotherapeutic drugs, such as paclitaxel, docetaxel, etoposide, teniposide, campopthecin, etc. have been developed from plant secondary metabolites [4]. To date, by conducting an extensive screening for anticancer activity in approximately 35,000 plants species, the National Cancer Institute (NCI) has built a database of 3,000 plant species with reproducible anticancer activity [5].

Among plants, bryophytes have been used in traditional medicine as a multi-purpose remedy for the treatment of injuries, inflammation, and fever [6–8]. A large number of

secondary metabolites have been purified and characterised in bryophytes [9], including several phenolic compounds, terpenoids, bibenzyls, and (bis)bibenzyls, which exhibited a wide range of potentially therapeutic properties, such as antioxidant, antibacterial, anti-inflammatory, and antitumour activity [6,10,11].

The first antitumour activity was reported by Belkin et al. 1952 [12], who found a weak activity of the ethanol and acid extract of *Polytrichum juniperinum* against implanted sarcomas. In 1977, the interest in antitumour properties of bryophytes started to increase when the NCI found that the extract of the moss *Polytrichum ohioense* was cytotoxic against KB cell culture, and in vivo activity in *Claopodium crispifolium* and *Plagiomnium venustum* [13,14]. Subsequently, Spjut et al. 1986 [15] summarised the results of the first comprehensive study by NCI on the antitumour properties of extracts from 123 mosses, 13 liverworts, and 1 hornwort species, and reported that 75 species showed varying degrees of cytotoxicity against P388 lymphocytic leukaemia cells. From that time onwards, numerous studies have found that mosses [16–26] and crude liverwort extracts [25,27–29] are cytotoxic for several cancer cell lines (Tables 1 and 2). The molecules responsible for the antiproliferative activity have been identified as terpenoids, bibenzyls, and macrocyclic (bis)bibenzyls, which are reported by various studies as cytotoxic for a wide range of cancer cells (Tables 1 and 2).

In this review, we report secondary metabolites from bryophytes that have demonstrated proapoptotic, antimitotic, MDR reversal, and antiangiogenic activity and can potentially contribute to the development of novel anticancer drugs.

2. The Hallmarks of Cancer

Cancer therapy relies on drugs that can target cellular processes called the hallmarks of cancer, such as apoptotic block, angiogenesis induction, resistance to chemotherapy (MDR), and cell cycle dysregulation [30]. In the following paragraphs, details concerning these peculiar cancer characteristics are discussed.

2.1. Multidrug Resistance in Cancer Cells

A well-known phenomenon in tumour therapy is multidrug resistance (MDR). MDR is mediated by the overexpression of several membrane proteins called ATP binding cassette transporters (ABC proteins), which operate an ATP-dependent efflux of chemotherapeutic drugs out of the cells. Currently, four ABC transporters are known to mediate the MDR: P-glycoprotein (P-gp), multidrug resistance associated protein (MRP1), lung resistance protein (LRP), and breast cancer resistance protein (BCRP) [31,32]. P-gp is the best known and well-characterised ABC transporter. P-gp can transport several hydrophobic amphipathic compounds, including drugs [33]. Typically, P-gp is expressed in most human tissues at low levels, although it is higher in excretory structures, such as large and small intestine apical epithelium, kidney proximal tubules, and liver bile ducts [34]. Moreover, P-gp is found to be overexpressed in several clinical tumours and is thought to be responsible for the unidirectional efflux of chemotherapy drugs out of tumour cells. Therefore, the overexpression of P-gp in cancer cells led to reduced intracellular drug concentrations, resulting in decreased cytotoxicity and poor therapeutic outcome.

2.2. Apoptotic Blockade

A second characteristic of cancer cells is the block of programmed cell death, which is called apoptosis. Apoptosis is a cell suicide program that eliminates unnecessary or unhealthy cells from the body during the development or after cellular stress [35]. Two main pathways lead cells to apoptotic death: Extrinsic and intrinsic pathways. The extrinsic pathway triggers apoptosis through caspase-8 and -10 after the extracellular interaction of specific ligands, such as tumour necrosis factor (TNF), with membrane receptors. The intrinsic pathway involves caspase-9 and activates mitochondrial outer membrane permeabilization (MOMP), causing the release of proapoptotic proteins [36]. Some antiapoptotic proteins include Bcl-2, Bcl-x, Bcl-XL, Bcl-XS, Bcl-w, BAG, and some

proapoptotic proteins include Bcl-10, Bax, Bak, Bid, Bad, Bim, Bik, and Blk [37]. The balance between pro- and antiapoptotic proteins is a fundamental determinant of the initiation of MOMP. In cancer cells, this balance is disrupted, causing blockage of the normal apoptosis process. In fact, cancer cells are continuously under stress conditions, such as hypoxia, genomic instability, DNA damage, oncogenic stress, which trigger apoptosis in normal cells. To overcome stress signals, cancer cells commonly overexpress antiapoptotic proteins, especially antiapoptotic proteins of the Bcl-2 family. This imbalance causes cancer cells to not respond to normal apoptotic stimuli. Therefore, drugs capable of stimulating apoptosis through the modulation of the underneath molecular processes are desirable. Several secondary metabolites from bryophytes have been reported to act on apoptosis agents, such as Bax, Bcl-2, caspase-3, and caspase-9 (Tables 1 and 2). Further details concerning the proapoptotic effects of the secondary metabolites of bryophytes are discussed in the following paragraphs.

2.3. Angiogenesis

An important process in cancer development and growth is the formation of new vessels, a process called angiogenesis [33]. Angiogenesis is a highly regulated process, involving several genes and their products, such as the vascular endothelial growth factor (VEGF) family, angiopoietins, transforming growth factors (TGF), platelet-derived growth factor, tumour necrosis factor-α, interleukins, and members of the fibroblast growth factor (FGF) family. The VEGF pathway is the dominant target for antiangiogenic drugs due to its ubiquitous and increased expression in most human cancers [38]. Pro- and antiangiogenic molecules can emanate from cancer cells, endothelial cells, stromal cells, blood, and the extracellular matrix. Their relative contribution is likely to change with the type and location of the tumour. Moreover, it is likely to change with tumour growth, regression, and relapse. Therefore, molecules that target angiogenesis could cause growth delay or even tumour death.

Table 1. List of secondary metabolites with known molecular targets in cancer cells.

Compounds	Chemical Class	Species	Cell Lines/Animal	Activity	References
Marchantin A	(Bis)bibenzyls	*Marchantia* ssp.	Mammary cancer cells MCF7	Cell growth inhibition; Apoptosis inducer; Cell cycle arrest;	[39]
			Human melanoma A375 cells	Cytotoxic;	[40]
			Breast cancer A256 cells Breast cancer T47D cells	Reduction in cell viability	[41]
			MCF-7	Increase in cleaved caspase-3, cleaved caspase-9, and cleaved PARP	
Marchantin C	(Bis)bibenzyls	*Marchantia* ssp.	T98G	P-gp inhibition; microtubules depolymerization; angiogenesis inhibition; cell migration inhibition	[42–46]
12-bromomarchantin C	Halogenated (bis)bibenzyl	Marchantia C synthetic derivative	PC-3	Tubulin depolymerization induction	[47]

Table 1. *Cont.*

Compounds	Chemical Class	Species	Cell Lines/Animal	Activity	References
Marchantin M	(Bis)bibenzyls	*Marchantia* ssp.	Human prostatic carcinoma PC-3 cells	Induction of apoptosis through ER stress	[48]
			Mice model with *APC* gene mutation	Apoptotic induction through caspase-3 and topoisomerase II inhibition; P-gp expression decrease; angiogenesis inhibition	[49]
Riccardin D	(Bis)bibenzyls	*Dumortiera hirsuta*	Human colon cancer HT-29 cells	Apoptosis inducer by suppressing the NF-kB signaling pathway	[50]
Riccardin D-26	(Bis)bibenzyls	Riccardin D synthetic derivative		Apoptosis induction; xenograft tumor growth inhibition; cell cycle regulator	[51]
3, 12, 30-Tri(2-(dimethylamino) ethoxy)-riccardin D	Tri-O-alkylated (bis)bibenzyls	Riccardin D synthetic derivative	A549	Lysosomal membrane permeabilization; apoptosis induction	[52]
13, 40-Bis((pyrrolidin-1-yl)methyl)-riccardin D	Amino methylated (bis)bibenzyls	Riccardin D synthetic derivative	A549	Lysosomal membrane permeabilization; apoptosis induction	[52]
10-bromoriccardin D	Halogenated (bis)bibenzyls	Riccardin D synthetic derivative	PC-3	Cell cycle arrest; tubulin depolymerization	[47]
Riccardin F	(Bis)bibenzyls	*Plagiochasma intermedium*	Myelogenous leukaemia K562 cells; multidrug resistant K562/A02	MDR reversal through P-gp inhibition	[53]
Plagiochin E	(Bis)bibenzyls	*Marchantia polymorpha*	K562/A02	MDR reversal through P-gp inhibition	[54]
12-bromoplagiochin E	Halogenated (bis)bibenzyls	Plagiochin E synthetic derivative	PC-3	Tubulin depolymerization	[47]
Isoplagiochin A	(Bis)bibenzyls	*Plagiochila fruticosa*	In vitro tubulin polymerization assay	Tubulin polymerization inhibition	[55]
Isoplagiochin B	(Bis)bibenzyls	*Plagiochila fruticosa*	In vitro tubulin polymerization assay	Tubulin polymerization inhibition	[55]
Brittonin A Brittonin B	Methoxylated bibenzyls	*Frullania inouei*	KB; KB/VCR; K562; K562/A02	Proliferation inhibition; MDR reversal	[56]
(±)-Radulapin D	Prenylated bibenzyl	*Radula apiculata*	PC-3	Apoptosis via ROS accumulation; Bax increase; caspase-9 increase	[57]
Ent-11α-hydroxy-16-kauren-15-one	Ent-kaurane diterpenoids	*Jungermannia* ssp.	H60 cells	With TNF-α inducing DNA fragmentation	[58]

Table 1. *Cont.*

Compounds	Chemical Class	Species	Cell Lines/Animal	Activity	References
Jungermannenone A-B	Ent-kaurane diterpenoids	*Jungermannia fauriana*	PC-3	Apoptosis via ROS accumulation; Induction of cell cycle arrest	[59]
Isomanool	Diterpenoids	*Heteroscyphus tener*	PC-3; DU145	Cell cycle arrest; caspase-3 increase; ROS accumulation	[60]
Lepidozin G	Triterpenoids	*Lepidozia reptans*	PC-3	Apoptosis through ROS accumulation; mitochondrial membrane potential disruption	[61]

Table 2. List of secondary metabolites with their cytotoxic activity against cancer cells.

Compounds	Chemical Class	Species	Cell Lines/Animal	Activity	References
Muscicolone	Diterpenoids	*Frullania muscicola*	KB, PG, HT-29, BEL-7402	IC_{50} 20–60 mg/mL	[62]
5α, 8α, 9α-trihydroxy-13E-labden-12-one; 5α, 8α-dihydroxy-13E-labden-12-one	Labdane diterpenoids	*Scapania undulate*	1) A549 2) K562 3) A2780	1) IC_{50} 37.6 µmol/L 2) IC_{50} 36.8 µmol/L 3) IC_{50} 19.5 µmol/L	
Scapaundulin C	Labdane diterpenoids	*Scapania undulate*	1) A549 2) K562 3) A2780	1) IC_{50} 39.2 µmol/L 2) IC_{50} 37.1 µmol/L 3) IC_{50} 16.8 µmol/L	[63]
**nn	Atisane diterpenoids	*Lepidolaena clavigera*	P388	IC_{50} 16 µg/mL	[64]
Notolutesin A	Diterpenoids	*Notoscyphus lutescens*	PC-3	IC_{50} 6.2 µM	[65]
Perrotettianal A	Diterpenoids	*Porella viridissima*	A2780 ovarian cancer cells	IC_{50} 1.6 µg/mL	[66]
Chiloscyphenols A	Sesquiterpenoids	*Bazzania albifolia*	MCF-7	IC_{50} 5.6 µM	[67]
Chandolide	Zierane sesquiterpene-γ-lactone	*Chandonantus hirtellus*	HL-60	IC_{50} 5.3 µg/mL	[68]
Anadensin	Zierane sesquiterpene-γ-lactone	*Chandonantus hirtellus*	HL-60	IC_{50} 17.0 µg/mL	
3,18,20-epi-iso-chandonanth-one	Diterpenoids	*Chandonantus hirtellus*	HL-60	IC_{50} 17.0 µg/mL	
13,18,20-epi-iso-chandonanthone	Diterpenoids	*Chandonantus hirtellus*	HL-60	IC_{50} 17.0 µg/mL	
(+)-3α-[4′Methoxybenzyl]-5,7-dimethoxyphthalide	Bibenzyls	*Frullania* ssp.; *Porella perrottetiana*	1) HL-60 2) KB	1) IC_{50} 0.92 µM 2) IC_{50} 0.96 µM	
(−)-3α-[3′-Methoxy-4′,5′-methylenedioxybenzyl]-5,7dimethoxyphthalide	Bibenzyls	*Frullania* ssp.; *Porella perrottetiana*	1) HL-60 2) KB	1) IC_{50} 6.30 µM 2) IC_{50} 5.47 µM	
Tulipinolide	Sesquiterpene lactone	*Frullania* ssp.; *Porella perrottetiana*	1) HL-60 2) KB	1) IC_{50} 4.59 µM 2) *nd	[69]

Table 2. *Cont.*

Compounds	Chemical Class	Species	Cell Lines/Animal	Activity	References
7-oxopinguisenol-12-methyl ester	Sesquiterpenoid	*Frullania* ssp.; *Porella perrottetiana*	1) HL-60 2) KB	1) IC_{50} 8.53 μM 2) IC_{50} 52.64 μM	
4α-5β-Epoxy-8-epiinunolide	Sesquiterpene lactone	*Frullania* ssp.; *Porella perrottetiana*	1) HL-60 2) KB	1) IC_{50} 2.68 μM 2) IC_{50} 46.27 μM	
(-)-herbertenediol	Sesquiterpenoids	*Mastigophora diclados*	1) HL cells 2)KB cells	1) IC_{50} < 5 μg/mL 2) IC_{50} > 10 μg/mL	[70]
(-)-a-Herbertenol	Sesquiterpenoids	*Mastigophora diclados*	1) HL cells 2)KB cells	1) IC_{50} > 10 μg/mL 2) IC_{50} > 10 μg/mL	
(-)-Diplohyllolide A	Sesquiterpenoids	*Mastigophora diclados*	1) HL cells 2)KB cells	1) IC_{50} < 5 μg/mL 2) IC_{50} < 5 μg/mL	
(3S,5S,7R,10S)-3-hydroperoxy-7-hydroxy-eudesma-4(15)-ene	Sesquiterpenoids	*Chiloscyphus polyanthus var. rivularis*	A549	Cytotoxic IC_{50} > 10 μM	[71]
Diplophyllolide	Sesquiterpene lactone	*Clasmatocolea vermicularis*	P388	IC_{50} 0.4 ug/ml	[72]
Scapairiin G Scapairrin H Scapairrin I Scapairrin J	Labdane diterpenoids	*Scapania irrigua*	MDA-MB231; A2780; HeLa; HT-29	IC_{50} < 10 μM (see reference for details)	[73]
Lycophlegmarinol B	Triterpenoids	*Lycopodium phlegmaria*	1) HuCCA-1 2) A549 3) HepG2 4) MOLT-3	1) Inactive 2) Inactive 3) Inactive 4) IC_{50} 14.7 μM	
Lycophlegmarinol D	Serratene triterpenoids	*Lycopodium phlegmaria*	1) HuCCA-1 2) A549 3) HepG2 4) MOLT-3	1) IC_{50} 26.72 μM 2) IC_{50} 47.5 μM 3)Inactive 4) IC_{50} 3.0 μM	[74]
21b-Hydroxy-serrat-14-en-3a-ol	Serratene triterpenoids	*Lycopodium phlegmaria*	1) HuCCA-1 2) A549 3) HepG2 4) MOLT-3	1) IC_{50} 2.62 μM 2) Inactive 3) IC_{50} 2.42 μM 4) IC_{50} 2.94 μM	
Lepidozin A	Cycloartane triterpenoids	*Lepidozia reptans*	1) PC-3 2) A549 3) H3255 4) H446	1) IC_{50} 6.5 μM 2) IC_{50} 7.0 μM 3) IC_{50} 9.4 μM 4) IC_{50} 7.5 μM	
Lepidozin F	Cycloartane triterpenoids	*Lepidozia reptans*	1) PC-3 2) A549 3) H3255 4) H446	1) IC_{50} 8.6 μM 2) IC_{50} 8.8 μM 3) Inactive 4) IC_{50} 9.6 μM	[61]
Naviculyn caffeate	Caffeate esters	*Bazzania novaezelandiae*	PP38 murine leukaemia cells	IC_{50} 1.1 μg/mL	[75]
(±)-Radulapin A (±)-Radulapin C (±)-Radulapin D (±)-Radulapin E (±)-Radulapin F (±)-Radulapin G (±)-Radulapin H	Prenylated Bibenzyl	*Radula apiculata*	PC-3 A549 MCF-7 NCI-H121199	IC_{50} < 10 μM (see reference for details)	[57]
2-carbomethoxy-3,5dihydroxystilbene	Bibenzyls	*Radula amoena*	1) HepG-2 2) SMMC-7721 3) A549	1) 22.5 μg/mL 2) 27.63 μg/mL 3) 18 μg/mL	[76]

Table 2. *Cont.*

Compounds	Chemical Class	Species	Cell Lines/Animal	Activity	References
3,5-dimethoxybibenzyl	Bibenzyls	*Radula amoena*	1) HepG-2 2) SMMC-7721 3) A549	1) 19.1 μg/mL 2) 18.49 μg/mL 3) 16.55 μg/mL	[76]
Perrotettin E	(Bis)bibenzyls	*Pellia endivifolia*	1) Promyelocytic HL-60 cells 3) Pro-monocytic Human myeloid leukaemia U-937 cells 4) Myelogenous leukaemia cell line K562 5) NT2/D1 6) A-172 7) U-251	1) IC_{50} 14.2 μM 2) IC_{50} 50.5 μM 3) IC_{50} 37.2 μM 4) IC_{50} 11.2 μM 5) IC_{50} 8.8 μM 6) IC_{50} 15 μM	[77]
10′-hydroxyperrottetin E	(Bis)bibenzyls	*Pellia endivifolia*	1) HL-60 2) U-937 3) K562 4) NT2/D1 5) A-172 6) U-251	1) IC_{50} > 100 μM 2) IC_{50} 38.5 μM 3) IC_{50} > 100 μM 4) IC_{50} 15.5 μM 5) IC_{50} 26.2 μM 6) IC_{50} 47.2 μM	[77]
10,10′-dihydroxyperrottetin E	(Bis)bibenzyls	*Pellia endivifolia*	1) HL-60 2) U-937 3) K562 4) NT2/D1 5) A-172 6) U-251	1) IC_{50} > 100 μM 2) IC_{50} > 100 μM 3) IC_{50} > 100 μM 4) IC_{50} 6.8 μM 5) IC_{50} 53.8 μM 6) IC_{50} 54.8 μM	[77]

*nd: Not determined; **nn: Not named

3. Methodology

The relevant literature was searched in the Scopus and Web of Science databases using "article, abstract, and keywords" as the search field. The literature was searched by typing in pairs of the following keywords: "antitumor" OR "anticancer" OR "antiproliferative" paired with "bryophytes" OR "liverworts" OR "mosses" OR "hornworts". For literature concerning the current state of in vivo research, the keyword "animal models" OR "mice" OR "rats" OR "in vivo" was added to the abovementioned keywords. To investigate the literature on secondary metabolites with antitumour activity in more detail, keywords "bibenzyls", "(bis)bibenzyls", "terpenes", and "terpenoids" (from here on, "specific compound classes") were used after the first screening.

4. Macrocyclic and Acyclic (Bis)bibenzyls

(Bis)benzyls are hydroxystilbenoid oligomers formed by two hydroxystilbenoid units. (Bis)bibenzyls are abundant secondary metabolites in liverworts, that together with mono, sesqui, and diterpenoids, are the chemical constituents of specific organelles of liverworts called oil bodies (Figure 1) [9,78]. More than 125 unique (bis)bibenzyls have been isolated and characterised in liverworts [9]. Several studies have shown that some of these (bis)bibenzyls possess omnifarious biological activities, such as antifungal, antioxidant, antibacterial, anti-inflammatory, and antitumour activities [6]. Further details concerning the anticancer properties of these molecules are discussed in the following paragraphs.

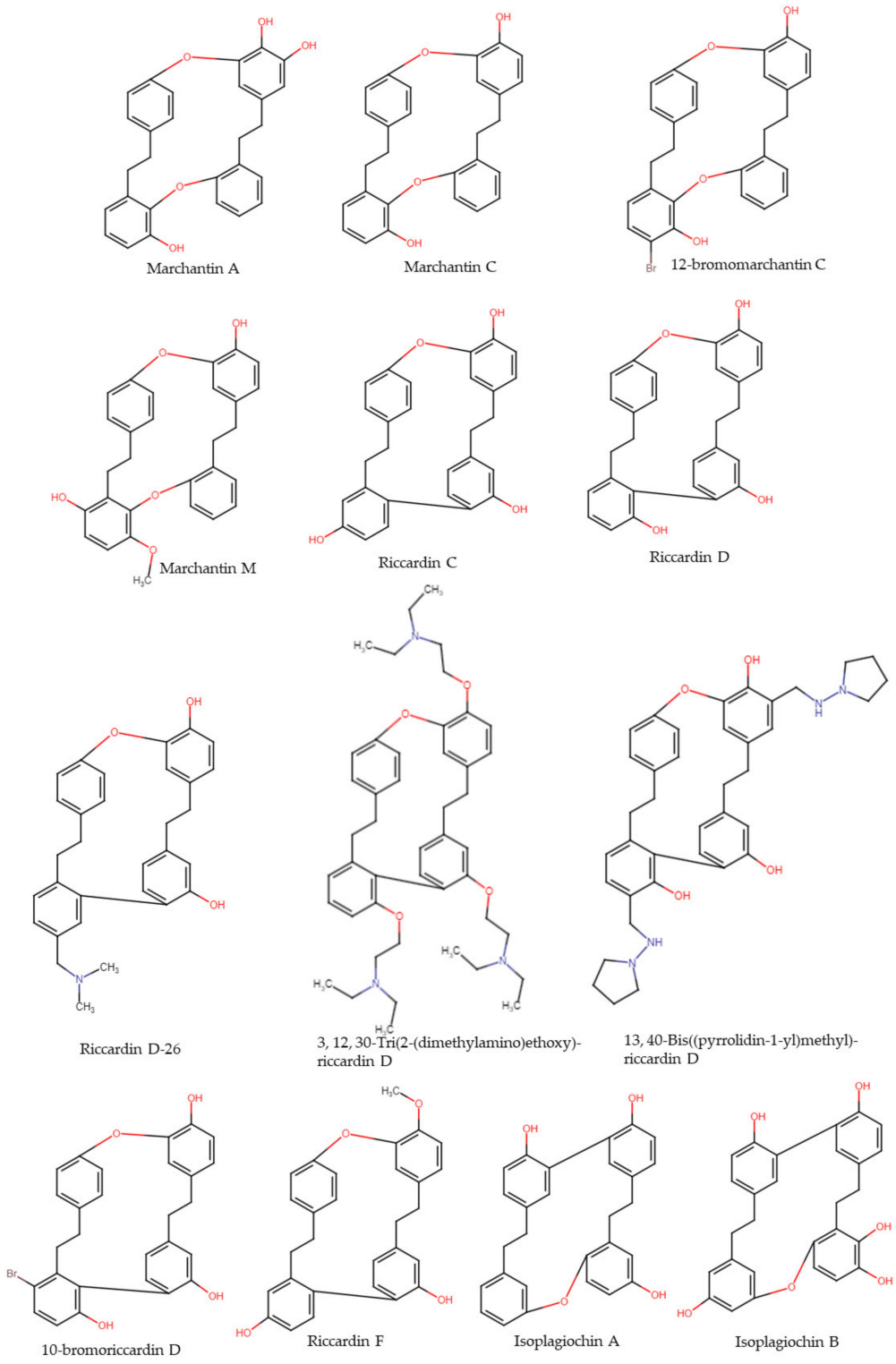

Figure 1. *Cont.*

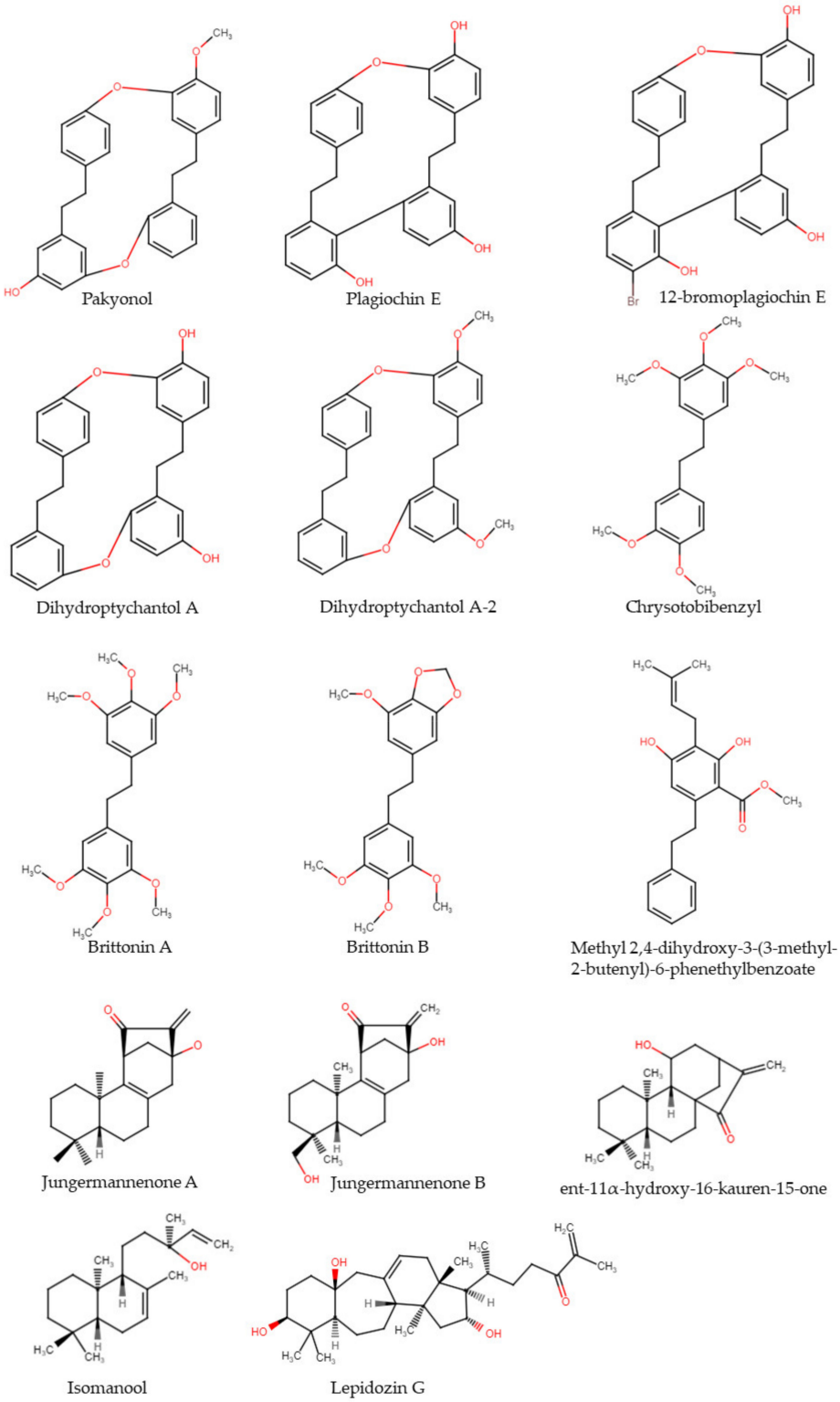

Figure 1. Structures of secondary metabolites from bryophytes.

4.1. Marchantin A

Marchantin A has been isolated from various liverwort species of the genus *Marchantia* [39,79–82] and *Wiesnerella denudata* [83]. Several studies have shown that marchantin A is cytotoxic and causes apoptosis and cell cycle arrest in cancer cells. An extensive investigation by Huang et al., 2010 [39] found that marchantin A induced apoptosis in MCF-7 breast cancer cells. In addition, Western blot analysis demonstrated a dose-dependent increase (from 2.5 to 10 μg/mL) in cleaved caspase-3, cleaved caspase-9, and cleaved poly (ADP ribose) polymerase (PARP), indicating a proapoptotic induction in MCF-7 cells. Moreover, the authors investigated the effects on the cell cycle regulators p21, p27, cyclin B1, and cyclin D1. The results showed that marchantin A had an effect on the cell cycle by inducing p21 and p27 gene expression in a dose-dependent manner (from 2.5 to 10 μg/mL), while suppressing cyclin B1 and D1 expression. Furthermore, marchantin A was cytotoxic with an IC_{50} value of 4.0 μg/mL.

Jensen et al. 2012 [41] confirmed the previous results, in which the measurement of cytotoxicity in the breast cancer cell lines A256, MCF-7, and T47D resulted in an IC_{50} value of 5.5 μM (A256), 11.5 μM (MCF-7), and 15.3 μM (T47D). The authors of [40] found that marchantin A was toxic to melanoma cells (A375) at a concentration of 25 μg/mL. Interestingly, marchantin A showed less toxicity to the normal keratinocyte cell line, indicating a specific effect on the malignant melanoma cell line. Taken together, this evidence indicates that marchantin A would be a suitable candidate for further anticancer drug development. However, further data concerning cytotoxicity for normal cell lines and animal models are required.

4.2. Marchantin C and Derivatives

Marchantin C has been isolated from several species of liverworts, such as *Marchantia polymorpha* [84], *Marchantia peleacea*, *Marchantia tosana* [85], *Dumortiera hirsute* [86], and *Reboulia hemisphaerica* [87]. Marchantin C has been extensively studied by several investigators, showing promising antitumour properties, such as P-gp inhibition, microtubule polymerization inhibition, angiogenesis, and cell migration inhibition.

Shi et al. 2008 [42] investigated marchantin C apoptosis induction through transmission electron microscopy, demonstrating apoptotic nuclei formation in human glioblastoma A172 cells treated with 16 μM of marchantin C for 24 h. Furthermore, the authors investigated the expression level of Bcl-2 and Bax through RT-PCR analysis and Western blot assay. Bax and Bcl-2 belong to the Bcl-2 family proteins, which are involved in the control of mitochondria-dependent intrinsic apoptotic pathways [88]. A bulk of research indicates that negative outcomes in cancer therapy are correlated with the overexpression of antiapoptotic proteins, such as Bcl-2 in several malignant tumours [89]. Following the marchantin C treatment by 24 h, Bax expression was dose-dependently upregulated, while Bcl-2 was downregulated, indicating the activation of proapoptotic Bax and inhibition of antiapoptotic Bcl-2.

The authors of [43] obtained similar results in xenografted nude mice treated with 10 and 20 mg/kg of marchantin C. Caspase-3 and Bax levels increased in mice treated with 20 mg/kg of marchantin C, while Bcl-2 levels decreased, indicating that the effects were also observed in the in vivo models. Furthermore, the authors demonstrated that marchantin C causes microtubule depolymerization in a dose-dependent manner in A172 and Henrietta Lacks cervical cancer cell line (HeLa) as well as nude mouse xenografts. Similar results were obtained in a tubulin polymerization assay with bovine brain tubulin, suggesting a direct interaction between marchantin C and tubulin.

Marchantin C has been reported to inhibit angiogenesis by Lv et al. 2012 [46]. The authors found that marchantin C (5 μM) inhibits (57% inhibition) human endothelial cells tube formation, which is induced by human glioblastoma T98G cells, while no significant inhibition was observed in human leukaemia monocytic THP1 cells.

Xi et al. 2010 [45] accomplished the synthesis of two synthetic marchantin C derivatives. The authors observed that marchantin C and its derivatives, MC2 and MC3, increased the vincristine toxicity in vincristine resistant human oral epithelial carcinoma KB/VCR cells, suggesting that marchantin C and its derivatives caused a reversal of multidrug resistance (MDR). Notably, MC2, a marchantin C dimethyl ether derivative, showed the strongest MDR reversal effect (from 2 to 8 μM). To support this hypothesis, the authors demonstrated that the fluorescent P-gp substrate ADR accumulated in the cytoplasm of cells treated with MC2. However, no modulation of the expression of the P-gp gene was observed. This evidence corroborates the hypothesis that marchantin C and its methyl derivatives could be a direct inhibitor of P-gp.

Jiang et al. 2012 [47] reported that the synthesis of marchantin C and two brominated derivatives, 10-bromomarchantin C and 12-bromomarchiantin C, exhibited a stronger cytotoxicity in KB, MCF-7, and PC-3 cells. Furthermore, 12-bromomarchantin C was able to induce tubulin depolymerization in PC-3 cells.

4.3. Marchantin M

Marchantin M has been isolated for the first time from the liverwort *Asterella angusta* [90]. Marchantin M was reported to induce endoplasmic reticulum stress by two independent studies [48,91]. Zhang et al. 2015 [48] reported that marchantin M reduced tumour growth in xenograft tumours in nude mice, and induced ER stress in PC-3 cancer cells. Jiang et al. 2013 [91] found that marchantin M acts as a non-competitive inhibitor of proteasome 26 s, causing ER stress due to the accumulation of misfolded and unfolded proteins. Furthermore, the authors reported that marchantin M inhibited PI3K activity and downregulated Akt gene expression, which caused the repression of the PI3K/Akt/mTOR pathway that activates the autophagy in PC-3 cancer cells, which is constitutively blocked.

4.4. Riccardin C

Riccardin C is a macrocyclic (bis)bibenzyls first isolated from the liverwort *Reboulia hemisphaerica* [92], and was found in various other species of liverworts, such as *Marchantia polymorpha* [93,94], *Marchantia palmata* [94], *Mastigophora dyclados* [95], *Dumortiera hirsute* [82], *Conocephalum conicum*, *Plagiochasma rupestre* [96], and *Ricciocarpos natans* [97]. Xu et al. 2010 [90] observed that riccardin C induced the expression of Bax and decreased the expression of Bcl-2 in a dose-dependent manner at 10 and 20 μmol/L after 24 h of treatment in prostate cancer cells (PC-3). Moreover, the authors observed that the caspase-3 and PARP cleavage through Western blot analysis proved the induction of apoptosis by the caspase signal pathway. These results suggest that riccardin C triggers responses similar to marchantin C, marchantin M, and plagiochin E [90]. Further investigations are required for in-depth activities, such as antimitotic as well as toxicity to normal cell lines and animal models.

4.5. Riccardin D and Derivatives

Riccardin D was first isolated and characterised in the liverwort *Monoclea forsteri* by Asakawa et al. 1995 [98]. Subsequently, it was found in *Dumortiera hirsuta* [99] and *Plagiochila cristata* [100]. Numerous studies have investigated the anticancer activities of riccardin D and its synthetic derivatives. To date, together with marchantin A and marchantin C, riccardin D is among the most investigated macrocyclic(bis)bibenzyl from bryophytes. Several studies have evidenced that riccardin D can induce apoptosis, modulate cell cycle, and inhibit angiogenesis and cell migration (Table 1). Research has revealed that riccardin D induces apoptosis through the caspase signal pathway [101], DNA topoisomerase II

inhibition [102], and NF-kB pathway suppression [50]. Xue et al. 2012 [102] found that riccardin D inhibits DNA topoisomerase II in human leukaemia cells HL-60, K562, and MDR K562/A02. Through the DNA relaxation assay, the authors showed that riccardin D blocked the relaxation of the supercoiled pBR322 DNA, suggesting topoisomerase II inhibition. Further investigations with flow cytometry analysis indicated that riccardin D did not significantly induce apoptosis in Topoll-deficient cells HL-60/MX2. Moreover, the authors observed a dose-dependent cleavage of caspase-3 and -9 as well as an increase in the Bax/Bcl-2 ratio.

Riccardin D has been shown to inhibit angiogenesis in xenografts of human lung carcinoma H460 mice [103]. The authors found that riccardin D injections (20 mg/kg) decreased the mean vascular density in mice xenograft tumours. Moreover, riccardin D caused the downregulation of angiogenesis-related genes VEGF, EGF, and MMP-2 in HUVEC cells. Other studies have measured the anticancer activities of synthetic derivatives of riccardin D. These studies are fundamental in finding chemical modifications that can enhance the biological activity of the original natural molecule.

An extensive investigation on riccardin D derivatives was carried out by Sun et al. 2017 [52]. The authors achieved the total synthesis of riccardin D and its aminomethylated, O-alkylated, and aminated derivatives to inquire about their structure–activity relationships (SARs). The results revealed that the aminomethylated and O-alkylated derivatives showed the highest cytotoxic activity, suggesting that the introduction of nitrogen-containing groups to riccardin D, which increased the total basicity of the molecule, is critical for improved cytotoxicity. In particular, the tri-O-alkylated derivative 3, 12, 30-tri(2-(dimethylamino)ethoxy)-riccardin D exhibited the most potent anticancer activity against the A549, MCF-7, and K562 cell lines, (IC_{50} values of 0.51, 0.23, and 0.19 mM), which was clearly superior to those of the parent compound riccardin D (IC_{50} values of 28.14, 18.31, and 17.56 mM, respectively). Similarly, the aminomethylated derivative 13, 40-bis((pyrrolidin-1-yl)methyl)-riccardin D showed IC_{50} values of 0.99, 0.43, and 0.80 mM. Furthermore, these derivatives were able to target lysosomes and induce permeabilization of the lysosomal membrane as well as apoptosis and necrosis in A549 cancer cells.

Jiang et al. 2012 [47] accomplished the total synthesis of riccardin D and two bromine derivatives. The bromine substitution on C12′ produced an inactive derivative ($IC_{50} > 50$ μM), while the C10-substituted bromine derivative, 10-bromoriccardin D, was stronger than its parent molecule (IC_{50} values of 5.9, 5.4, and 5.6 μM vs. 7.1, 6.6, and 10.1 μM) against KB, MCF-7, and PC-3 cell lines, respectively. Flow cytometry analysis revealed that 10-bromoriccardin D caused cell cycle arrest in the G_2/M phase (30.10% at 10 μM). Further investigations with immunofluorescence microscopy demonstrated that after the treatment of PC-3 with 6, 8, and 10 μM for 24 h, the 10-bromoriccardin D induced a stronger tubulin depolymerization than riccardin D. Molecular modelling suggests that 10-bromoriccardin D can dock tubulin in the same binding site of the colchicine. However, no data on cytotoxicity in normal cell lines or animal models are available.

4.6. Riccardin F

Riccardin F has been isolated and characterised from the liverwort *Plagiochasma intermedium* [53,104]. Through the flow cytometry analysis and MTT assay, Ji et al. 2011 [53] showed that riccardin F significantly increased ADR accumulation and toxicity (IC_{50} value of 2.34 ± 0.54 μg/mL) with respect to ADR alone (IC_{50} value of 5.78 ± 0.76 μg/mL) in MDR myelogenous leukaemia A562/A02 cells. Moreover, the authors found that subtoxic concentrations of riccardin F (3 μg/mL) induced the accumulation of ADR and rhodamine-123 (Rh-123), a P-gp substrate, indicating that riccardin F can modulate the P-gp protein.

4.7. Isoplagiochin A and B

Isoplagiochin A and B were isolated and characterised for the first time by Hashimoto et al. 1994 [105] in the liverwort *Plagiochila fruticosa*. Similar to marchantin C, both isoplagiochin A and B have exhibited the ability to inhibit in vitro tubulin polymerization with IC_{50} values of of 50 and 25 μM, respectively [55]. The authors found that the saturated derivatives dihydroisoplagiochin A and B did not show activity against tubulin polymerization (IC_{50} > 100 μM), proposing that the unsaturated C7′-C8′ bond is crucial for tubulin interaction. However, as previously reported, marchantin C does not have the C7′-C8′ unsaturation, which also causes inhibition. Therefore, further research is required to understand the structure–activity relationship of macrocyclic (bis)benzyl–tubulin interactions.

4.8. Plagiochin E and Derivatives

Plagiochin E was first isolated and characterised in the liverwort *Marchantia polymorpha* [106]. In a study by Shi et al. 2008 [54], plagiochin E was found to increase the cytotoxicity of adriamycin in a dose-dependent manner in MDR K562/A02 cells with the highest activity at 8 μg/mL (adriamycin IC_{50} value of 0.68 ± 0.09 μg/mL). Moreover, flow cytometric investigations revealed a dose-dependent accumulation of Rh-123 after a 60-min treatment of K562/A02 cells with plagiochin E at 4 and 8 μg/mL. On the contrary, no significant accumulation of Rh-123 was observed in the normal K562 phenotype. Furthermore, after 24 h of incubation with 2, 4, and 8 μg/mL of plagiochin E, the expression level of P-glycoprotein measured through fluorescent anti-Pgp monoclonal antibodies was decreased in a dose-dependent manner by 12.7, 30.4, and 45.3%, respectively. Interestingly, a plagiochin E structurally-related marchantin C derivative did not affect the P-gp gene expression, indicating that although similar, these molecules could act on different cellular constituents. Moreover, plagiochin E (5 and 10 μmol/L), similar to other macrocyclic(bis)benzyls, has exhibited proapoptotic properties by activating caspase pathways and modulating the Bax/Bcl-2 ratio in PC-3 cancer cells [90]. The total synthesis of plagiochin E and its brominated derivatives was obtained by Jiang et al. 2012 [47]. The two plagiochin E derivatives, 12-bromoplagiochin E and 12,17-dibromoplagiochin E, demonstrated significant cytotoxicity to KB, MCL-7, and PC-3 cells than plagiochin E. Further experiments with immunofluorescence microscopy evidenced that 12-bromoplagiochin E was able to induce tubulin depolymerisation.

4.9. Pakyonol

Flow cytometry analysis and the MTT assay showed that the (bis)bibenzyl pakyonol isolated from the liverwort *Plagiochasma intermedium* significantly improved ADR accumulation and toxicity (IC_{50} value of 1.21 ± 0.41 μg/mL) compared to ADR alone (IC_{50} value of 5.78 ± 0.76 μg/mL) in MDR A562/A02 cells [53]. Subtoxic concentrations of pakyonol (3 μg/mL) induced the accumulation of ADR and Rh-123, suggesting inhibition of the P-gp protein [53]. In another research, pakyonol with a concentration of 20 μM, was found to induce apoptosis in PC-3 cancer cells, but had a weaker effect than riccardin C, marchantin M, and plagiochin E [90].

4.10. Dihydroptychantol A and Derivatives

Dihydroptychantol A (DHA) isolated from the liverwort *Asterella angusta* has demonstrated a dose-dependent cytotoxicity enhancement of adriamycin, vincristine, and paclitaxel in adriamycin-resistant K562/A02, vincristine-resistant KB/VCR, and paclitaxel-resistant cellosaurus H460/tax cells at concentrations of 5, 10 and 20 μM [107]. On the contrary, the MDR reversal effect was not significant in all of the non-MDR cell lines, indicating that DHA could modulate the P-gp protein. Western blot analysis evidenced that DHA decreased the expression of P-gp, suggesting that macrocyclic (bis)benzyls could reverse the MDR, thus lowering the P-gp expression. Furthermore, the authors tested the MDR reversal effect of two O-methylated DHA and C7′-C8′ dehydrogenated derivatives (Figure 1). With respect to DHA, the three derivatives exhibited a lower MDR reversal

effect, suggesting that both the O-methylated hydroxyls and the stilbenoid C7′-C8′ double bond in the structure have a minimal effect in the reversal of MDR cells. However, the cytotoxicity of the DHA derivatives was not investigated. In a study by Pang et al. 2014 [108], the de novo synthesised O-methylated DHA derivative (DHA2) was reported to affect autophagy-related events, including the inhibition of Akt/mTOR and XIAP and the induction of LC3B-II in several ovarian cancer cell lines. The Western blot analysis has shown that a DHA2 treatment for 24 h resulted in noticeably decreased levels of XIAP and Bcl-2 and increased levels of Bax.

5. Bibenzyls

The bibenzyls are (bis)bibenzyls related metabolites, which consist of one hydroxystilbenoid unit. Some studies have reported certain degrees of cytotoxicity against several cancer cell lines [57,76] (Table 2). In particular, the prenylated bibenzyls Radulapin A-H from *Radula apicata*, 2-carbomethoxy-3,5dihydroxystilbene and 3,5-dimethoxybibenzyl from *Radula amoena* have exhibited cytotoxic activity against several cancer cell lines (Table 2).

5.1. Brittonin A, B, and Chrysotobibenzyl

Brittonin A and B are methoxylated bibenzyls isolated and characterised from the liverwort *Frullania inouei* [56]. After 24 h of treatment with both brittonin A and B, vincristine cytotoxicity in KB/VCR increased from 3.19 to 10.91 (5 μM), and adriamycin cytotoxicity in K562/A02 increased from 4.40 to 8.26 (5 μM). In the same study, chrysotobibenzyl showed the most potent MDR reversal activity toward both KB/VCR and K562/A02 cells.

5.2. (±)-Radulapin D

(±)-Radulapin D, a prenylated bibenzyl isolated from the liverwort Radula apiculate, [57] induced apoptosis in PC-3 cells after a 24-h treatment at a concentration of 6 μM (62.6% apoptotic cells stained with annexin V/propidium iodide). Further flow cytometric investigation indicated that (±)-radulapin D caused a substantial increase in ROS levels in a dose-dependent manner (2, 4, 6 μM) with a significative ROS accumulation at 6 μM. Furthermore, the measure of mitochondrial membrane potential (MMP $\Delta\Psi m$) revealed that (±)-radulapin D caused a loss of 100, 86.3, 66.5, and 2.6% $\Delta\Psi m$. Subsequently, Western blot analysis has shown that (±)-radulapin D caused an increase in the proapoptotic Bax protein, caspase-9, and poly-ADP-ribose polymerase (PARP) cleavage in a dose-dependent manner. The results suggested that (±)-radulapin D induces the mitochondrial-mediated apoptosis pathway in PC-3 cells and disrupts the mitochondrial functions via increasing ROS levels and decreasing the mitochondrial membrane potential.

6. Terpenoids

Terpenoids are a large group of secondary metabolites of plants, consisting of various linked isoprene units containing different functional groups and represent a rich reservoir of candidate compounds for drug discovery. The multiplicity of ways in which isoprene units can be combined and rearranged allows the existence of about 25,000 different chemical terpenoid structures [109]. Therefore, this multitude of chemical structures is subdivided into several subclasses, based on the number of isoprene units: Hemiterpenoids (C5), monoterpenoids (C10), homoterpenoids (C11,16), sesquiterpenoids (C15), diterpenoids (C20), sesterpenoids (C25), triterpenoids (C30), tetraterpenoids (C40), and polyterpenoids (C > 40, higher-order terpenoids) [110]. Bryophytes are rich in terpenoids and several of them have been isolated and characterised in different species, mainly liverworts [78]. Increasing numbers of terpenoids have exhibited anticancer activities both in vitro and in vivo, due to ROS accumulation, cell cycle arrest, and mitochondrial induced apoptosis [109,111]. Several sesquiterpenoids [67–72], diterpenoids [60,63–66,68], and triterpenoids [61,74] isolated from bryophytes have demonstrated in vitro cytotoxic activity (ranging from weak to strong) against a considerable number of cancer cell lines (Table 2).

Among these molecules, the diterpenoids jungermannenone A, jungermannenone B, ent-11α-hydroxy-16-kauren-15-one (KD), isomanool, and the triterpenoid lepidozin G have been shown to induce apoptosis, cell cycle arrest by ROS accumulation, and subsequent DNA damage in several cancer cell lines(Table 1, Figure 1). Further details concerning these molecules are discussed in the following paragraphs.

6.1. Jungermannenone A and B

An extensive investigation by Nagashima et al. 2003 [112] screened 44 *ent*-kaurane diterpenoids isolated from *Jungermannia fauriana* and found that the exo-methylene cyclopentanone moiety was necessary for the cytotoxic activity. In addition, the C13-hydroxyl group was responsible for an increase in cytotoxicity. The results led to the selection of two ent-kaurane diterpenoids, jungermannenone A and B, which exhibited the highest cytotoxic activity against several cancer cell lines (Table 1) [59,112]. A subsequent study by the same group [59], showed that both jungermannenone A (JA) and B (JB) were able to arrest the cell cycle, induce apoptosis, and cause mitochondrial damage. JA (1.5 μmol/L) caused a significant increase in PC-3 apoptotic cells (5.34% at 0 h and 30.11% at 24 h). Similar results were observed in PC-3 cells treated with 5 μmol/L JB (5.41% at 0 h and 30.11% at 24 h). Western blot analysis revealed that both JA and JB activated the cleavage of caspase-3 and PARP at concentrations of 1.5 and 5 μmol/L in a time-response manner with a significant activation after 12 h of treatment, indicating apoptosis induction through the caspase-3 signalling pathway. Furthermore, in JA and JB, a significant accumulation of ROS after 2 h of treatment was observed. The results evidenced that JA and JB were able to induce apoptosis in PC-3 cells. JA was a stronger inducer with respect to JB, suggesting that the lack of 18-hydroxyl moiety in JA resulted in higher hydrophobicity, and thus higher bioavailability.

6.2. Ent-11α-hydroxy-16-kauren-15-one

A recent study found that ent-11a-hydroxy-16-kauren-15-one (KD) isolated from the liverwort *Jungermannia truncata* [113] has demonstrated NF-kB activity inhibition and a synergistic effect on the induction of apoptosis, when combined with tumour necrosis factor-α (TNF-α) or camptothecin (CPT) [113,114]. The authors found that KD and TNF-a at the non-cytotoxic concentrations of 0.5 mM and 5 ng/mL, respectively, had a synergistic cytotoxic effect on HL-60 cells. Furthermore, co-treatments with KD (0.5 μM) and TNF-a (5 ng/mL) for 18 h increased the appearance of DNA ladders and chromatin condensation in 24% of the treated cells and the cleavage of PARP, indicating an enhanced activation of the apoptosis. Similar results were achieved when KD was combined with CPT. The results suggest that KD could be used in combination with other chemotherapeutics to enhance the apoptosis induction.

6.3. Isomanool

A study by Lin et al. 2014 [60] found that isomanool isolated from the liverwort *Heteroscyphus tener* can arrest the cell cycle in the G0/G1 phase and induce apoptosis via caspase-3 and -9 activation and ROS accumulation in both prostate cancer cell lines, PC-3 and DU145. Flow cytometry analysis evidenced that the percentage of PC-3 cells in the G0/G1 phase were 73 and 82% at concentrations of 10 and 20 μM isomanool compared to 66% in the control cells. A similar number of DU145 cells were in the G0/G1 phase, 68 and 75% compared to 63% in control cells. Molecular investigations through Western blot analysis indicate that cyclin D1, cyclin E, and cyclin-dependent kinase 4 (Cdk4) were reduced after the treatment with isomanool in a time-dependent manner in PC-3 and DU145 cells, while p21 was upregulated in both cells. These results suggested that isomanool arrests the cell cycle interfering with cyclin D1 and E expression, which prevents the formation of the Cdk4/cyclin D1 complex that is essential for the facilitation of the cell cycle process [115]. The same study demonstrated that isomanool can induce apoptosis in both cell lines. Flow cytometry analysis showed that the apoptotic cells accumulated in a

time-dependent manner from 8.02 to 70.25% and 4.22 to 23.75% in PC-3 and DU145 cells, respectively. Fluorometric analysis and Western blot indicated a time dependent increase in cleaved caspase-3 and -9 and cleaved-PARP in both PC-3 and DU145 cells after 12 h of treatment with 20 μM of isomanool. Furthermore, the activation of caspase-9 and -3 led the researchers to investigate the production of ROS. After 30 min of treatment with 20 μM isomanool, a significant increase in ROS was observed.

6.4. Lepidozin G

A study by Zhang et al. 2021 [61] found that lepidozin G isolated from the liverwort *Lepidozia reptans* caused apoptosis and ROS accumulation mitochondrial dysfunctions in PC-3 cells. The authors treated PC-3 cells with 5 μM lepidozin G for 24 h, observing an increase in the percentage of annexin V-positive cells (41.1%) against 2.1% in control cells. The authors measured ROS accumulation after the treatment with lepidozin G (1.25, 2.5, 5, and 10 μM), observing a significant dose-dependent ROS accumulation, which is clearly observable at the lowest concentration (1.25 μM). These results indicated that lepidozin G caused a loss ΔΨm in PC-3 cells (85.2, 71.5, and 16.8%) at concentrations of 2, 4, and 6 μM for 24 h, respectively. Furthermore, the results suggested that lepidozin G can stimulate apoptosis through ROS increase and mitochondrial membrane potential disruption, indicating the activation of the intrinsic apoptotic pathway.

7. Discussion and Concluding Remarks

Cancer chemotherapy relies on drugs that can target a distinct set of cell processes called the hallmarks of cancer, such as resistance to cell death, angiogenesis induction, resistance to chemotherapy, cell migration, and cell cycle dysregulation [30]. Interestingly, as reported in this review, several bibenzyls, (bis)bibenzyls, and terpenoids isolated from bryophytes have shown the ability to modulate these processes (Table 1). To date, the toxicity of secondary metabolites of bryophytes in normal cell lines or in vivo animal models is still poorly investigated. Therefore, more research should be addressed to screen the in vitro and in vivo genotoxicity and hepatotoxicity of secondary metabolites of bryophytes. Furthermore, epigenetic alterations of oncogenes and tumour suppressor genes (TSG) underlie tumorigenesis in many human cancer types. Several natural compounds (polyphenols, carotenoids, etc.) are able to act as epigenetic modulators [116,117]. For this reason, further studies should be carried out to evaluate whether some of these biological activities described could be attributable to a possible epigenetic action exerted by the second metabolites present in the bryophytes, as demonstrated for other compounds of natural origin.

As a result from the reviewed literature, studies have mainly focused on the antiproliferative activities of liverworts and mosses. There are approximately 300 species of hornworts, and only a few have been studied biochemically [118]. Apart from the study by Spjut et al. 1986 [15], in which one hornwort species was tested and found to be inactive, no subsequent investigation has explored the antiproliferative potential of hornworts. Therefore, further investigation of the chemical composition and antiproliferative properties of hornworts could lead to the discovery of new interesting anticancer molecules.

Several molecules are known to reverse MDR through P-gp interaction, although no clinical drug has been developed yet, which makes the discovery of new anti-MDR compounds still desirable. As evidenced in this review, the secondary metabolites of several bryophytes have been reported to modulate P-gp activity, causing resistance reversal, and thus increasing the accumulation of common chemotherapeutics in cancer cells, such as vincristine and adriamycin. However, data are based only on in vitro studies, while the in vivo resistance reversal potency of bryophytes anticancer agents has not yet been investigated.

Generally, one limiting trait related to many plant secondary metabolites is their poor solubility or poor bioavailability that delays the manufacturing of large amounts required to serve as medicines, which makes it difficult for use as drugs. Different approaches are taken to enhance solubility and bioavailability of plant-derived molecules, such as the use of semi-synthetic or synthetic analogues, lipid formulations (i.e., solid lipid nanoparticles, microemulsions, nanoemulsions), and synthetic nanoparticles delivery [119]. To date, no investigation has dealt with the study of alternative delivery strategies, making it necessary to direct studies to deepen this aspect. Moreover, the collection of adequate amounts of secondary metabolites for research purposes is often hampered by the lack of a considerable quantity of plant material. Several researchers accomplished the total synthesis of different secondary metabolites of bryophytes and their derivatives. Notably, some derivative molecules, such as marchantin C, riccardin D, and plagiochin E derivatives exhibited stronger anticancer activities with respect to their parent compounds. Further investigations on novel structure modifications could lead to the discovery of even more potent derivatives, from which new drugs could be developed. In conclusion, the present review showed that bryophytes could provide new molecules for the discovery and development of novel anticancer drugs.

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