Review

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Marchantia polymorpha as a Source of Biologically Active Compounds

Filip Nowaczyński [1,*], Rosario Nicoletti [2,*], Beata Zimowska [3] and Agnieszka Ludwiczuk [1]

[1] Department of Pharmacognosy with the Medicinal Plant Garden, Medical University of Lublin, 20-093 Lublin, Poland; filip.nowaczynski@umlub.pl (F.N.); agnieszka.ludwiczuk@umlub.pl (A.L.)

[2] Council for Agricultural Research and Economics, Research Center for Olive, Fruit and Citrus Crops, 81100 Caserta, Italy; rosario.nicoletti@crea.gov.it (R.N.)

[3] Department of Plant Protection, University of Life Sciences, 20-400 Lublin, Poland; beata.zimowska@up.lublin.pl (B.Z.)

* Correspondence: rosario.nicoletti@crea.gov.it and filip.nowaczynski@umlub.pl

Abstract: *Marchantia polymorpha* L., also known as common liverwort or umbrella liverwort, is a spore-forming plant belonging to Marchantiaceae family. This thallose liverwort has gained importance as a model plant, mainly because of its global distribution, and easy and rapid in vitro culturing. A review of the literature shows that the dominant compounds in this species are undoubtedly sesquiterpenoids and bisbibenzyls. Among sesquiterpenoids it is worth to mention cuparenes, chamigranes and thujopsanes. Compounds belonging to these classes were found in specimens from Japan, China, Poland, Germany, and India, and could be the chemical markers of this liverwort species. The most characteristic compound occurring in *M. polymorpha* is a macrocyclic bisbibenzyl, marchantin A. Marchantin-type aromatic compounds together with other bisbibenzyls, such as riccardin D, isoriccardin C or perrottetin E were proven to withhold antifungal and antibacterial properties in various studies. Marchantin A is structurally similar to tubocurarine, exhibiting myorelaxant activity. Its antioxidant and cytotoxic effects have also been confirmed. In this review we summarize the current knowledge on the diversity of compounds produced by *M. polymorpha*, emphasizing chemical variability depending on the origin of the plant material. Moreover, the biological activity of extracts obtained from this liverwort species as well as single secondary metabolites are described.

Keywords: common liverwort, terpenoids, bisbibenzyls, biological activity, Marchantiaceae.

1. Introduction

Bryophytes are terrestrial spore-bearing plants that comprise three phyla: liverworts (Marchantiophyta), mosses (Bryophyta), and hornworts (Anthocerophyta). These small, nonvascular plants are phylogenetically placed between algae and ferns and are considered the first inhabitants of terrestrial habitats [1]. As the first land plants, they were often exposed to adverse environmental conditions; hence, their ability to synthesize many different specialized secondary metabolites is extremely high. Indeed, such 'chemical weapons' are necessary for these small plants, since they lack mechanical protection like higher vascular plants [2]. Among the bryophytes, the chemical constituents of the Marchantiophyta and their biological activity have been studied in great detail. Over the last 40 years, more than 3,000 compounds have been found in this group of plants. Many of these products are characterized by unprecedented structures, and some, including the pinguisane-type sesquiterpenoids and the sacculatane-type diterpenoids, have not been found in any other plants, fungi or marine organisms. This unique chemical composition increases the number of potential applications in medicine and beyond. The secondary metabolites of this group of spore-bearing plants have a huge, not yet fully understood potential, as phytotherapeutics or natural pesticides. The available literature data indicate that constituents occurring in liverworts show

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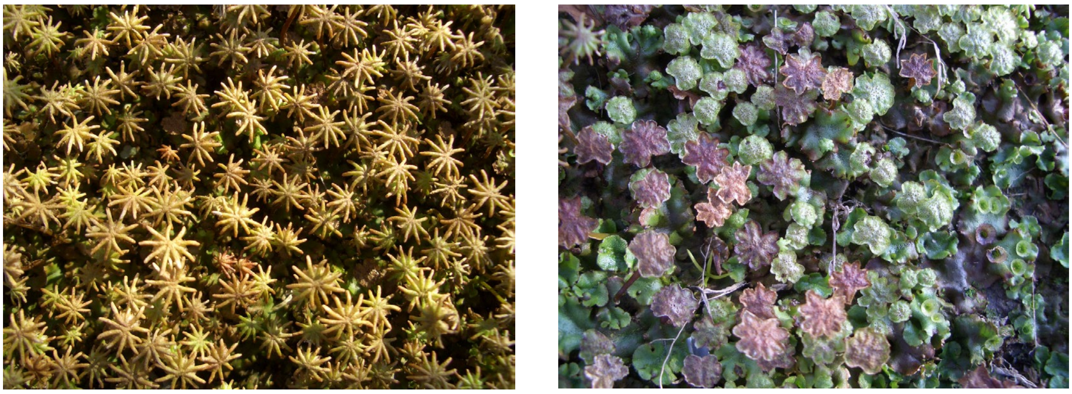
interesting biological activities, such as antibacterial, antifungal, cytotoxic, insect repellant, as well as some enzyme inhibitory and proapoptotic activities [3–5].

Marchantia polymorpha L., also known as common liverwort or umbrella liverwort, belonging to Marchantiaceae family (Figure 1), is the most widely distributed liverwort in the world. It is a cosmopolitan species that occurs from tropical to arctic regions [6,7].



(**a**) (**b**)

Figure 1. *Marchantia polymorpha* – umbrella liverwort: (**a**) female and (**b**) male plant. (Photos by Prof. Yoshinori Asakawa, Tokushima Bunri University, Japan)

Marchantia polymorpha has also been shown to consist of cryptic or nearly cryptic species based on isozyme, RFLP (nrDNA), and RAPD markers in a survey of plants from North America, Europe and Asia. Three taxa were identified and recognized as subspecies which differ in habitat, although they sometimes occur sympatrically [8]. More detailed analyses conducted by Linde and his associates [9] revealed a more complex pattern with evidence suggesting hybridization and introgression between subspecies. Such heterogeneity within a single species of any plant, brings with its variability in chemical composition and, consequently, biological properties. The aim of this paper is to review the available scientific literature concerning both the chemical composition and the biological properties of the most well-known liverwort species, *M. polymorpha*. Special attention was paid to the variability of the chemical composition depending on the origin of the plant material.

2. Chemical Diversity of *M. polymorpha*

Liverworts (Marchantiophyta) are plants that produce a wide array of biologically active secondary metabolites. These compounds are accumulated in the oil bodies, which are prominent and highly distinctive organelles uniquely found in liverworts [10]. Oil bodies are present in 95% of all liverwort species and are intracellular organelles bounded by a single unit membrane originating from dilated endoplasmic reticulum cisternae, containing lipophilic globules [11]. In the thallose liverworts like *M. polymorpha*, oil bodies are confined to scattered idioblastic oil body cells while oil bodies of leafy liverworts are generally present in all cells [12]. The number, size, and colour of oil bodies are species specific. Oil bodies are estimated to serve a protective role for the plant, with their contents postulated to protect the plant against various biotic and abiotic stressors [13].

A review of the literature on the chemical composition of the umbrella liverwort shows that it is characterized by great diversity. The following groups of chemical compounds have been identified so far in *Marchantia*: mono-, sesqui- and diterpenoids, sterols and triterpenoids, bibenzyls, bisbibenzyls, phenanthrene derivatives, flavonoids, lipids and other compounds (Table 1).

Table 1. Metabolites found in *Marchantia polymorpha.*

No.	Compounds	Formula	Plant origin	References
		MONOTERPENOIDS		
1	Limonene	$C_{10}H_{16}$	USA (axenic culture)	[14]

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		SESQUITERPENOIDS		
2	◎-Acoradiene	$C_{15}H_{24}$	Poland	[15]
3	◎-Neocallitropsene	$C_{15}H_{26}$	Poland	
4	◎-Alaskene	$C_{15}H_{24}$	Poland	[15]
5	Acorenone B	$C_{15}H_{24}O$	Poland	[15]
6	◎-Gurjunene	$C_{15}H_{24}$	New Zealand, USA (axenic culture)	[14,16]
7	Aromadendrene	$C_{15}H_{24}$	Turkey	[17]
8	◎-Barbatene	$C_{15}H_{24}$	Japan	[18]
9	◎-Barbatene	$C_{15}H_{24}$	Japan	[18–20]
10	◎-Chamigrene	$C_{15}H_{24}$	Japan, Germany, India	[19–22]
11	◎-Chamigrene	$C_{15}H_{24}$	Germany, India, Poland, USA (axenic culture)	[14,15,19,21–24]
12	*ent*-9-oxo-◎-Chamigrene (Laurencenone C)	$C_{15}H_{22}O$	Japan, Germany, Poland	[20,21,23]
13	Cuparene	$C_{15}H_{24}$	Turkey, Japan, Poland, USA (axenic culture)	[14,15,17,18,24]
14	◎-Cuprenene	$C_{15}H_{24}$	Japan, Poland	[15,20]
15	◎-Cuprenene	$C_{15}H_{24}$		[19]
16	◎-Cuprenene	$C_{15}H_{24}$	Japan	[20]
17	◎-Cuprenene	$C_{15}H_{24}$	Japan, Poland	[15,20]
	◎-Microbiotene	$C_{15}H_{24}$	Poland	[15]
18	2-Cuparenol (= Cuparophenol, ◎-Cuparenol)	$C_{15}H_{22}O$	Turkey, South Africa	[17,18,23,25]
19	*ent*-Cuprenenol	$C_{15}H_{26}O$		[19]
20	Cyclopropanecuparenol	$C_{15}H_{26}O$	Japan, Poland	[15,19,20]
21	*epi*-Cyclopropanecuparenol	$C_{15}H_{26}O$	Poland	[15,19]
22	◎-Selinene	$C_{15}H_{24}$	New Zealand, Poland	[15,16]
23	*ent*-◎-Selinene	$C_{15}H_{24}$	India	[19,22]
24	◎-Eudesmol	$C_{15}H_{26}O$	Turkey	[17]
25	(2*Z*,4*E*)-Abscisic acid	$C_{15}H_{20}O_3$		[26]
26	(2*E*,4*E*)-Abscisic acid	$C_{15}H_{20}O_3$		[26]
27	*ent*-Thujopsene	$C_{15}H_{24}$	Japan, Poland, USA (axenic culture)	[14,15,18–20,27]
28	*ent*-Thujopsan-7◎-ol	$C_{15}H_{26}O$	Japan, Germany	[20,21]
29	*ent*-Thujopsenone (= Thujops-3-en-5-one)	$C_{15}H_{22}O$	Japan	[18–20]
30	Bicycloelemene	$C_{15}H_{24}$		[19]
31	◎-Elemene	$C_{15}H_{24}$		[19,28]

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32	◎-Elemene	$C_{15}H_{24}$		[19]
33	◎-Elemene	$C_{15}H_{24}$		[23,24]
34	Eremophilene	$C_{15}H_{24}$		[28]
35	1(10),11-Eremophiladien-9◎-ol	$C_{15}H_{24}O$	Germany	[29]
36	Costunolide	$C_{15}H_{20}O_2$	Japan	[30]
37	◎-Himachalene	$C_{15}H_{24}$	USA (axenic culture)	[14,24]
38	◎-Bisabolene	$C_{15}H_{24}$		[19]
39	◎-Caryophyllene	$C_{15}H_{24}$		[19]
40	◎-Cedrene	$C_{15}H_{24}$		[19]
41	7-epi-◎-Cedrene	$C_{15}H_{24}$	Poland	[15]
42	◎-Cedrene	$C_{15}H_{24}$		[28]
43	◎-Herbertenol	$C_{15}H_{22}O$	Japan, Poland	[15,18,19]
44	ent-◎-Herbertenol	$C_{15}H_{22}O$	Germany	[21]
45	Widdrol	$C_{15}H_{26}O$	Japan	[18,19]
		DITERPENOIDS		
46	Marchanol	$C_{20}H_{32}O_2$	Vietnam	[31]
47	Labda-7,13*E*-dien-15-ol	$C_{20}H_{34}O$		[19,27,32]
48	Vitexilactone	C22H34 O4	Vietnam	[31]
49	Phytol	$C_{20}H_{40}O$	South Africa, Poland	[15,19,33]
		STEROLS and TRITERPENOIDS		
50	Campesterol	$C_{28}H_{48}O$	South Africa, Germany, India	[21,22,33,34]
51	Brassicasterol	$C_{28}H_{46}O$		[23]
52	Dihydrobrassicasterol	$C_{28}H_{48}O$		[34,35]
53	Stigmasterol	$C_{29}H_{48}O$	South Africa, Germany	[21,33]
54	Sitosterol	$C_{29}H_{50}O$	South Africa, Germany	[21,33,34]
55	Clionasterol (24◎-ethyl)	$C_{29}H_{50}O$		[34,35]
56	12-Oleanene-3-one	C30H48 O	Vietnam	[31]
57	Ursolic acid	C30H48 O3	Vietnam	[31]
58	3,11-Dioxoursolic acid	C30H44 O4	Vietnam	[31]
		BIBENZYLS		
59	Lunularin	$C_{14}H_{14}O_2$	Germany, Vietnam	[19,21,31]
60	Lunularic acid	$C_{15}H_{14}O_4$	Cell culture, Japan Germany	[36–38]
61	Prelunularic acid	$C_{15}H_{16}O_5$		[38–40]
62	2,5-Di-*O*-◎-D-glucopyranosyl- 4′-hydroxybibenzyl	$C_{26}H_{34}O_{13}$		[41]

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63	2-[3-(Hydroxymethyl) phenoxy]-3-[2- (4-hydroxyphenyl) ethyl]phenol	$C_{21}H_{20}O_4$	China	[42]
	BISBIBENZYLS			
64	Riccardin C	$C_{28}H_{24}O_4$	South Africa, India, Vietnam	[22,31,33]
65	Riccardin D	$C_{28}H_{24}O_4$	China	[43]
66	Riccardin H	$C_{31}H_{28}O_4$	China	[43]
67	Isoriccardin C	$C_{28}H_{24}O_4$	India, Vietnam	[22,31]
68	Isoriccardin D	$C_{28}H_{24}O_4$	China	[42]
69	13,13′-*O*-Isopropylidenericcardin D	$C_{31}H_{28}O_4$	China	[43]
70	Polymorphatin A	$C_{28}H_{24}O_4$	China	[42]
71	Marchantin A	$C_{28}H_{24}O_5$	China, Germany, India, Japan, Serbia (natural and cultured), Vietnam	[19,21,22,24,27,31,43–47]
72	7′,8′-Dehydromarchantin A	$C_{28}H_{24}O_4$	Serbia (cell culture)	[44]
73	Marchantin B	$C_{28}H_{24}O_6$	China Germany Japan	[19,21,27,43,45,46]
74	Marchantin C	$C_{28}H_{24}O_4$	South Africa, Germany, India, Japan, Serbia (cell culture)	[19,21,22,27,33,44–46]
75	Marchantin D	$C_{28}H_{24}O_6$	Germany, India, Japan	[19,21,22,27,45,46,48]
76	Marchantin E	$C_{29}H_{26}O_6$	China, Germany, India, Japan, Serbia (cell culture)	[19,21,22,27,43–46]
77	Marchantin F	$C_{28}H_{24}O_7$	South Africa,	[33]
78	Marchantin G	$C_{28}H_{22}O_6$		[48]
79	Marchantin H	$C_{28}H_{24}O_5$	South Africa,	[33]
80	Marchantin J	$C_{30}H_{28}O_6$	China, Germany	[21,42]
81	Marchantin K	$C_{29}H_{26}O_7$	Germany, Vietnam	[21,31]
82	Marchantin L	$C_{28}H_{24}O_6$	Germany	[21]
83	Isomarchantin C	$C_{28}H_{24}O_4$	India	[22]
84	Neomarchantin A	$C_{28}H_{24}O_4$	China	[43]
85	Perrottetin E	$C_{28}H_{26}O_4$	China, India	[22,42]
	OTHER AROMATICS			
86	3R-(3,4-Dimethoxybenzyl)-5,7-dimethoxyphthalide	C19H20 O6	Vietnam	[31]
87	Marchatoside	C20H22 O7	Vietnam	[31]

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88	3-(3,4-Dihydroxyphenyl)- 8-hydroxyisocoumarin	$C_{15}H_{10}O_5$	Germany (cell culture)	[37]
89	2,3-Dimethoxy-7-hydroxy-phenanthrene	$C_{16}H_{14}O_3$	Germany (cell culture)	[37]
90	2,7-Dihydroxy-3-methoxy-phenanthrene	$C_{15}H_{12}O_3$	Germany (cell culture)	[37]
91	3,3′-Dimethoxy-2,2′,7,7′-tetra-hydroxy-1,1′-biphenanthrene	$C_{30}H_{22}O_6$	Germany (cell culture)	[37]
92	2-Hydroxy-3,7-dimethoxy phenanthrene	$C_{16}H_{14}O_3$	India	[22]
93	*m*-Hydroxybenzaldehyde	$C_7H_6O_2$	Germany	[21]
94	*p*-Hydroxybenzaldehyde	$C_7H_6O_2$	South Africa, Germany	[21,33]
95	3-Methoxy-2,2′,3′,7,7′-pentahydroxy- 1,1′-biphenanthrene	$C_{29}H_{20}O_6$	Germany (cell culture)	[37]
96	2,2′,3,3′,7,7′-Hexahydroxy- 1,1′-biphenanthrene	$C_{28}H_{18}O_6$	Germany (cell culture)	[37]
97	2-(3,4-Dihydroxyphenyl)-ethyl-◎-D-allopyranoside	$C_{14}H_{20}O_8$		[41]
98	2-(3,4-Dihydroxyphenyl)-ethyl-◎-D-glucopyranoside	$C_{14}H_{20}O_8$		[41]
99	2-(3,4-Dihydroxyphenyl)-ethyl-*O*-◎-L-rhamnopyranosyl-(1→2)-◎-D- allopyranoside	$C_{20}H_{30}O_{12}$		[41]
100	2-(3,4-Dihydroxyphenyl)-ethyl-*O*-◎-D-xylopyranosyl-(1→6)-*O*-◎-D-allopyranoside	$C_{19}H_{28}O_{12}$		[41]
101	Salidroside	$C_{14}H_{20}O_7$		[49]
102	◎-(3,4-Dihydroxyphenyl)ethyl-*O*-◎-D-glucoside	$C_{14}H_{20}O_8$	Germany (cell culture)	[37,49]
103	Indole acetic acid	$C_9H_7O_2N$		[26]
		FLAVONOIDS		
104	Apigenin	$C_{15}H_{10}O_5$	Germany (cell culture); New Zealand	[37,50,51]
105	Apigenin-7-O-◎-D-glucuronide	$C_{21}H_{18}O_{11}$	New Zealand	[50,51]
106	Apigenin-7,4'-di-O-glucuronide	$C_{27}H_{26}O_{17}$	New Zealand	[50,51]
107	Luteolin	$C_{15}H_{10}O_6$	Germany	[21,50,51]

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108	Luteolin-7-O-◎-D-glucuronide	$C_{21}H_{18}O_{12}$	New Zealand	[50,51]
109	Luteolin-7,3'-di-O-◎-glucuronide	$C_{27}H_{26}O_{18}$	New Zealand	[50,51]
110	Luteolin-7,4'-di-O-◎-glucuronide	$C_{27}H_{26}O_{18}$	New Zealand	[50,51]
111	Luteolin-3'4'-di-O-◎-glucuronide	$C_{27}H_{26}O_{18}$	New Zealand	[50,51]
112	Luteolin-3'-O-◎-glucuronide	$C_{21}H_{18}O_{12}$	New Zealand	[50,51]
113	Luteolin-7,3'4'-tri-O-◎-glucuronide		New Zealand	[50,51]
114	Artemetin	C20H20 O8	Vietnam	[31]
115	Kaempferol	$C_{15}H_{10}O_6$	Vietnam	[31]
116	Quercetin	$C_{15}H_{10}O_7$	Vietnam	[31]
117	Aureusidin-6-O-g1ucuronide	$C_{21}H_{18}O_{12}$	New Zealand	[52]
118	5,3′,4′-Trihydroxyisoflavone- 7-*O*-◎-D-glucopyranoside (= Orobol-7-*O*-glucoside)	$C_{21}H_{20}O_{11}$		[41]
119	Riccionidin A	$C_{15}H_9O_6$		[53]
120	Riccionidin B	$C_{30}H_{17}O_{12}$		[53]
		LIPIDS		
121	Palmitic acid (16:0) (= Hexadecanoic acid)	$C_{16}H_{32}O_2$	Cell culture Japan, sporophyte	[20,54]
122	Ethyl palmitate (= Hexadecanoic acid ethyl ester)	$C_{18}H_{36}O_2$	Japan, sporophyte	[20]
123	Stearic acid (18:0) (= Octadecanoic acid)	$C_{18}H_{36}O_2$	Cell culture	[54]
124	Palmitoleic acid (16:1n-7) (= 9-Hexadecenoic acid)	$C_{16}H_{30}O_2$	Cell culture	[54]
125	Oleic acid (18:1n-9) (= 9-Octadecenoic acid)	$C_{18}H_{34}O_2$	Cell culture	[54]
126	Linoleic acid (18:2n-6) (= 9,12-Octadecadienoic acid)	$C_{18}H_{32}O_2$	Japan, sporophyte Cell culture	[20,54]
127	◎-Linolenic acid (18:3n-3) (= 9,12,15-Octadecatrienoic acid)	$C_{18}H_{30}O_2$	Cell culture	[54]
128	Arachidonic acid (20:4n-6) (= 5,8,11,14-Eicosatetraenoic acid)	$C_{20}H_{32}O_2$	Cell culture	[54,55]
129	EPA (20:5n-3)	$C_{20}H_{30}O_2$	Cell culture	[54,55]

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	(= Eicosapentaenoic acid)			
130	Oxacycloheptadecan-2-one	$C_{16}H_{30}O_2$	Japan, sporophyte	[20]
	OTHER COMPOUNDS			
131	Shikimic acid 4-(⊚-D-xylopyranoside)	$C_{12}H_{18}O_9$		[41]

As shown in Table 1, phytochemistry of *M. polymorpha* varies depending on its place of origin. The major chemical compounds, contributing to phytochemical complexity of this species, are distributed among two groups: terpenoids, and a second one including bibenzyls and bis-bibenzyls.

2.1. Terpenoids

Marchantia polymorpha is a rich source of terpenoids, in particular those belonging to the sesquiterpene group. The first sesquiterpenoid reported from *M. polymorpha* was *(S)*-2-hydroxycuparene (= 2-cuparenol). Isolation was conducted in 1974 by Hopkins and Perold [25] from a South African specimen. Two cuparane-type alcohols, cyclopropanecuparenol and its epimer, are the major volatile components present in this species. Both compounds are usually present in specimens from European countries, while in Japan only cyclopropanecuparenol is present. Besides the mentioned alcohols, other cuparanes are present in *M. polymorpha*, namely cuparene and α-, β-, γ- and δ-cuprenene. Thujopsanes and chamigranes are other sesquiterpenoids characteristic of *M. polymorpha*. They are represented by thujopsene, thujopsan-7β-ol, thujopsenone, α- and β-chamigrene, as well as *ent*-9-oxo-α-chamigrene [13,18].

Occasionally *M. polymorpha* can produce metabolites characteristic of a single specimen. In the Polish collection of *M. polymorpha*, acorane-type sesquiterpenoids were identified. The presence of α-neocallitropsene, acorenone B, β-alaskene, and β-acoradiene were confirmed [15]. Another example comes from Vietnamese specimens, which produce characteristic diterpenoids. In fact, Van Nguyen and coworkers [31] isolated marchanol, which belongs to the clerodane-type compounds, as well as vitexilactone from the labdane group.

Marchantia polymorpha does not synthesize monoterpenes. However, during cell culture at the initial stage of growth, it produces limonene [14].

2.2. Bibenzyls and Bisbibenzyls

Bibenzyls are organic compounds with a C6-C2-C6 skeleton which are synthesized by the phenylpropanoid pathway, like polyphenols [56]. Common liverwort is reported to produce only a few compounds, and among them it is worth to mention lunularin and lunularic acid [22,25,57]. Both metabolites are direct precursors in the biosynthesis of marchantin C, a bis-bibenzyl, which is later transformed to form marchantin A [58].

Bisbibenzyls are macrocyclic organic compounds, consisting of two bibenzyl units. Acyclic bisbibenzyl compounds are linked once, while the cyclic ones are linked twice. The most important bisbibenzyl found in *M. polymorpha* is marchantin A. It is derived from lunularic acid, with two ether linkages between C_6 – $C_{2'}$ and between C_{14} – $C_{11'}$ (Figure 1). The majority of common liverwort specimens contain marchantin A in large amounts. In fact, it was reported to be present in common liverwort from various countries, such as Japan, Germany, India, Hungary, Vietnam, China and Serbia [21,22,42,44,57,59–61]. This, however, is not true for South African *M. polymorpha* which, according to some studies, does not contain marchantin A at all [33]. Its place as the major cyclic bisbibenzyl was found to be taken by marchantin H. Moreover, marchantin E has been isolated form Indian and French specimens [5]. Marchantin A is also commonly found in many other plants from the Marchantiales [62,63] and other Marchantiophyta [64].

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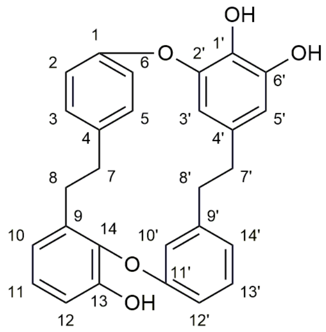

Figure 1. Chemical structure of marchantin A.

Riccardins are another group of cyclic bisbibenzyl compounds present in *M. polymorpha*. Japanese and Indian specimens of *M. polymorpha* contain riccardin C [13,21,41]. Riccardin H, isoriccardin D and 13,13′-O-isopropylidenericcardin D were found in *M. polymorpha* from China [57]. Isoriccardin C was found in Chinese, Indian and Vietnamese plant material [13,57,65].

Other bisbibenzyls that can be found in common liverwort are perrottetin E and polymorphatin A. Perrottetin E is an acyclic bisbibenzyl, found in Indian and Chinese specimens of common liverwort [13,57]. It can be used as a precursor for the synthesis of marchantin and riccardin type compounds [33]. Polymorphatin A is a cyclic compound, linked with one ether C_1–$C_{2'}$ linkage and one biphenyl C_{12}–$C_{12'}$ linkage. This bisbibenzyl was first found in Chinese *M. polymorpha* [57].

2.3. Other Compounds Found in M. polymorpha

Flavonoids are ubiquitous minor components in the Marchantiophyta, including *M. polymorpha* [3,4,60]. The main flavonoid types present in this species are flavone O-glucuronides. Luteolin, apigenin and their derivatives are the most abundant, as shown in Table 1.

Another interesting feature of *M. polymorpha* is the presence of polyunsaturated fatty acids, arachidonic acid (ARA, 20:4n-6) and eicosapentenoic acid (EPA, 20:5n-3). Shinmen et al. [55] have reported that culture of M. *polymorpha* contained high amounts of ARA and EPA (92 and 48 mg L^{-1}, respectively) under photomixotrophic conditions.

Among other components present in *M. polymorpha*, it is worth to mention sterols and triterpenoids, phenanthrenes, phthalides and other aromatic compounds. The sterols and triterpenoids found in common liverwort are similar to those found in higher plants. Among sterols, the presence of sitosterol and stigmasterol was confirmed, while among triterpenoids the occurrence of ursane and oleanane type compounds was reported [21,31,33]. Phenanthrene derivatives were found in the field collection of *M. polymorpha* from India [22], as well as form cell cultures of this liverwort growing in Germany [37]. The presence of two phthalides, 3R-(3,4-dimethoxybenzyl)-5,7-dimethoxyphthalide and marchatoside was confirmed in a Vietnamese collection [31].

3. Biological Activities

Common liverwort has a long history in ethnomedicine [62]. It was used as an antipyretic, antihepatic, antidotal and a diuretic medicinal plant [66].

Extracts of *M. polymorpha* were repeatedly proven to possess antifungal properties [43,67–70]. Many fungi are susceptible to growth inhibition when subjected to these extracts, including *Candida albicans* [67], *Tilletia indica*, *Fusarium oxysporum* f.sp. *lini*, *Sclerotium rolfsii*, *Rhizoctonia solani* [43,68], *Alternaria solani* [68], *Fusarium solani* [69] and *Aspergillus niger* [70]. Studies of activity against *C. albicans* determined that neomarchantin A, riccardin D and 13,13′-*O*-isopropylidene-riccardin D are the most effective compounds, while marchantin A, B, E and riccardin H, even if possessing some antifungal activity, were not as effective [67]. The activity also varies depending on the solvent used for extraction. Riccardin D (called by the authors plagiochin E), found in Chinese *M. polymorpha*, exhibits inhibitory properties against *C. albicans*, which were increased when combined with fluconazole [71].

Antibacterial activity of extracts from *M. polymorpha* is also an important subject of studies on common liverwort's activity. Besides the crude extracts, marchantin A also exhibits such properties [72]. It has an inhibiting effect on growth of both Gram-positive and Gram-negative bacteria, such as *Acinetobacter calcoaceticus*, *Bacillus cereus*, *Bacillus megaterium*, *Bacillus subtilis*, *Cryptococcus neoformans*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Pasteurella multocida*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Staphylococcus aureus*, *Staphylococcus epidermis*, *Streptococcus pyogenes* and *Streptococcus viridans* [22,43,60,70,73]. Lines of *M. polymorpha* were also subjected to genetic engineering, in order to obtain a mutant with a higher potential for the synthesis of antibacterial compounds [74].

In vitro studies show that many compounds isolated from *M. polymorpha* exhibit cytotoxic activity. A study conducted in 2008 showed that marchantin A induces growth inhibition on the breast cancer cell lines A256, MCF7 and T47D. The effect was increased when marchantin A and an Aurora-A kinase inhibitor were used simultaneously [75]. Marchantin A also demonstrated cytotoxicity against the malignant melanoma cell line A375, while having less cytotoxic activity against keratocytes and not affecting tyrosinase activity in a model assay [76]. In a recent study, common liverwort extracts showed effectiveness against a colon cancer cell line [77]. This is also true for hepatocellular carcinoma cells [78]. Other compounds with cytotoxic properties, that could be found in *M. polymorpha*, are marchantins B-D, neomarchantins A and B [79].

Marchantin A exhibits DNA polymerase β inhibitory activity, anti-HIV activity [80], and anti-influenza activity [81], the latter one postulated to be caused by its targeting of PA endonuclease. This compound is also postulated to exhibit antiprotozoal [81] and antitrypanosomal [82] activities. In fact, it showed in vitro growth inhibition against erythrocytic stages of *Plasmodium falciparum*, and strains of *Trypanosoma cruzi, Trypanosoma brucei rhodesiense* or *Leishmania donovani*. However, marchantin A has a low sensitivity index towards the aforementioned parasites, so the therapeutic window is rather narrow. Other compounds contained in *M. polymorpha*, such as marchantin E and plagiochin A showed antitrypanosomal activity, but at a less significant level than marchantin A [71].

While tested for its antioxidant properties, marchantin A showed free radical scavenging ability [73,83,84], depending on its concentration. It also ties in to the anti-inflammatory properties of *M. polymorpha*, originating in its ethnomedicinal uses. Marchantin A demonstrates inhibitory effect on 5-lipoxygenase and cyclooxygenase, a key enzyme in the arachidonic acid cascade [84]. The strength of this effect is structure dependent, as marchantin D, which had been tested in the same study, exhibited lower inhibition toward 5-lipoxygenase.

Chloroform extract of *M. polymorpha* was postulated to have hepatoprotective properties [85]. When mice were administered with paracetamol in liver-damaging quantities along with marchantin A, the amount of markers of liver damage in mice blood (aspartate transaminase and alanine transaminase) was significantly lower than in the control group administered with paracetamol only, and on par with the group in which paracetamol was administered along with silymarin. Another study showed that flavonoids of *M. polymorpha* can protect liver cells from injuries caused by administration of carbon tetrachloride [86]. As both compounds induce damage to liver cells with their oxidizing potential, the hepatoprotective effect was postulated to be due to antioxidant properties of *M. polymorpha* extracts.

Marchantin A, riccardin A, marchantin B and other compounds from *M. polymorpha* also have inhibitory effect on lipopolysaccharide production induced by nitric oxide [87]. As nitric oxide is postulated to play a role in the etiology of chronic neurodegenerative diseases [88], this property should be more closely investigated in the future.

Structural similarity between cyclic bisbibenzyl compounds and bisbenzylisoquinoline alkaloids, such as tubocurarine, has led to the investigation of muscle relaxation properties of marchantin-type compounds [89]. In a study published in 1995 [90], marchantin A was used in comparison to cepharanthine, a muscle relaxant. Both compounds expressed similar properties and were bound to a common receptor, which points to the muscle-relaxing properties of marchantin A likely being owed to the binding of calcium molecules. This may also be tying in with the inhibition by marchantin A of calmodulin [91], a protein with activity related to calcium levels in the cell.

4. Conclusions and Future Perspectives

Marchantia polymorpha is a very interesting case study. This liverwort is present in almost all environments, and has a very versatile phytochemical profile, including bisbibenzyl content. As we managed to summarize in our article, therapeutic potential of *M. polymorpha* is yet to be fully explored, but even now it holds potential for many future studies, which may be resulting in crucial findings.

The secondary metabolites of *M. polymorpha* endophytes show applicative potential as well. They exhibit selective cytotoxicity toward HeLa, RKO and FaDu cancer cell lines and antiviral properties [15,92] calling for more accurate investigations on their occurrence and bioactivities. As of late, our team is trying to establish the optimal ways to cultivate these bryendophytes, extract and evaluate their products.

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