



PHYTOCHEMICAL, USE IN ETHNOMEDICINE, AND THERAPEUTIC ACTIVITIES OF MARCHANTIA GENUS

FITOKIMIA, PENGGUNAAN DALAM ETNOMEDISIN, DAN TERAPI GENUS MARCHANTIA

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ABSTRACT

Background: Liverworts are a group of plants from the *Marchantia* genus containing various biologically active compounds and comprised of 65 species worldwide. This plant species belongs to the *Marchantiaceae* family, which was used empirically in China, North America, Ancient Greece, and Indonesia to treat open wounds, burns, hepatotoxicity, and infection prevention. Now, liverworts have great potential as medicinal and nutraceutical products. **Purpose:** Focuses on secondary metabolites obtained from the thalloid and whole plant parts (herbs) and the compilation of their pharmacological activities, which are still poorly documented. **Review:** This review article obtained related information through extensive international journals (online) scientific databases and offline (books) related to all searches of the species of the genus *Marchantia* which included: phytochemical content (secondary metabolites) and various pharmacological activities which were collected and compared all results of literature studies from various aspects. Some of the secondary metabolites are *Marchantin A, B, D dan E; Paleatin B; Perrottetin F, and Plagiochin E*, which have various pharmacological activities. Various results regarding all the therapeutic properties of the genus *Marchantia* have been produced in the world such as: anti-bacterial, anti-fungal, antioxidant, cytotoxic activity, anti-inflammatory, cardiogenic, hepatoprotective, muscle relaxant, antiosteoporosis, and skin care. **Conclusion:** Therefore, the potential for the development of medicinal, supplementary and nutraceutical products from various *Marchantia* species is very large and broad for the future.

ABSTRAK

Latar belakang: Lumut hati adalah kelompok tumbuhan dari genus *Marchantia* yang mengandung berbagai senyawa aktif biologis dan terdiri dari 65 spesies di seluruh dunia. Jenis tumbuhan ini termasuk dalam famili *Marchantiaceae*, digunakan secara empiris di Cina, Amerika Utara, Yunani Kuno, dan Indonesia untuk mengobati luka terbuka, luka bakar, hepatotoksitas, dan pencegahan infeksi. Saat ini, lumut hati memiliki potensi besar sebagai obat dan produk nutrasetikal. **Tujuan:** Berfokus pada metabolit sekunder yang diperoleh dari tallus dan seluruh bagian tanaman (herbal) dan kompilasi aktivitas farmakologisnya, yang masih kurang terdokumentasi. **Tinjauan pustaka:** Artikel ulasan ini memperoleh informasi terkait melalui pencarian ekstensif jurnal internasional (*online*) database ilmiah. Salah satu metabolit sekundernya adalah *Marchantin A, B, D dan E; Paleatin B; Perrottetin F, dan Plagiochin E*, yang memiliki berbagai aktivitas farmakologis. Berbagai hasil penelitian terkait khasiat terapeutik dari genus *Marchantia* telah dihasilkan di seluruh dunia seperti: anti-bakteri, anti-jamur, antioksidan, aktivitas sitotoksik, anti-inflamasi, kardiogenik, hepatoprotektor, relaksan otot, antiosteoporosis, dan perawatan kulit. **Kesimpulan:** Oleh karena itu, potensi pengembangan produk obat, suplemen dan nutrasetikal dari berbagai spesies *Marchantia* sangat besar dan luas untuk masa depan.

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INTRODUCTION

Diseases or abnormal conditions in metabolism or other health disorders in living things, including humans, come from damages to the physiological system that cause a decrease or loss of function of biomolecules in cells and tissues so that normal biological responses do not occur. The management of the health of a community/ country with a curative approach can sometimes cause new problems such as the cost of medicinal products. Individual health can also be maintained continuously with preventive, promotive, and rehabilitative approaches (Hossain *et al.*, 2013)

Various natural ingredients as part of medicine have been used all over the world for various therapeutic effects on diseases since ancient times, thus have become an integral part of the ethnomedicinal system of medicine in various regions of the world, including China, Ayurvedic, Greek, and Indonesia (Jamu) with only slight differences based on community culture (Adom, 2018; Coritico and Amoroso, 2020; WHO, 1998). Medicinal products from herbal ingredients that have become part of pharmaceutical products with preventive, promotive, rehabilitative to curative benefits can now be formulated into pharmaceutical products themselves. The various herbal ingredients are not only used as pharmaceutical products, but also used as nutraceutical products, and supplements that have higher promotional value because of their functions and dosage forms that attract consumers for their usage, safety, efficacy and quality requirements (Rijai, 2019). Various species and certain plant parts play an important role in preventing, alleviating, and treating several diseases; they are stored and can be found in various library sources, one of which can be found in the Indonesian Herbal Pharmacopoeia book (Pamungkas *et al.*, 2019). Thus, medicinal products from natural ingredients and nutraceuticals as preventive and curative efforts in health management are the most effective strategies, and are preferred by many people (Rijai, 2019; Suprapti *et al.*, 2018)

Moss plants (*bryophytes*) contain 24,000 species worldwide, but they are not considered significant enough for the economic improvement. Moss as one type of plant that is widely used traditionally in the world, including in Indonesia meets daily needs as food and herbal medicine, either harvested directly from nature or cultivated. There is still a shortage of various processed products from liverworts for food products, nutraceuticals, supplements, and medicinal product preparations. Thus, it is sufficient for researchers around the world to do extensive experimental research on mosses, so that they can be processed into products that have a higher selling value or increase the impact of the economic value of various liverwort herbal plants (Maigoda *et al.*, 2022; Purkon *et al.*, 2021a). Further, the reason also comes from its relatively small size and biomass. Indonesia uses many natural plant resources as potential medicinal products; one of which is the

liverworts of the *Marchantia* genus (Fadhilla *et al.*, 2012; Pamungkas *et al.*, 2019). *Marchantia* is a genus of liverworts that can be easily found throughout the world. In recent years, global research has been carried out on the *Marchantia* species. *Marchantia* species in various classical Greek references/ medical records have been used as a valuable plant in applications to heal open wounds as a prevention of bacterial infections, inflammatory wounds, external wounds, snake antivenom, and a remedy for liver dysfunction. The genus *Marchantia* based on scientific literature is believed to be a primitive lineage of land plants on our planet earth millions of years ago, thus becomes important in the genetic history of plant descent (Bowman, 2016; Viet *et al.*, 2022).

The literature method approach of this study is a comprehensive and extensive review of information by using the literature search method on several scientific articles and reference books/ e-books related to the genus *Marchantia* and related species. Phytochemical content (secondary metabolites) and pharmacological activity were collected online through a search of scientific databases, including Elsevier (Mendeley), EBSCO, Crossref, Springer, DOAJ, and Google Scholar. While the offline literature used includes books and e-books (Parihar and Balekar, 2016). The preliminary written introduction contains the background, various studies of supporting/ comparative literature, the formulation of the problem, and the purpose of the literature study/ review of this article. Various literature study materials containing various explanations are reviewed and compared in terms of time, the time span for taking the scientific articles under study, the place where the research is carried out, the techniques/ methods used, and the design of the literature study.

This scientific literature study presents several secondary metabolites from liverworts of the genus *Marchantia*, which are potential pharmaceutical products with various pharmacological activities for health maintenance to healing.

LITERATURE STUDY

The results of literature studies have shown that the details of the pharmacological activities associated with species of *Marchantia* are still poorly documented. Thus, we have tried to collect information about therapeutic efficacy based on the content of secondary metabolites of this genus *Marchantia*, which in the future has great potential as a medicinal/ nutraceutical product whose dosage form can increase the product marketability to the world market because of its function to improve health status.

Liverworts of the *Marchantia* genus in Indonesia can be obtained from several places; one of them is from the Research Center for Plant Conservation and Botanical Gardens - Cibodas Botanical Gardens (KRC) - LIPI, Cianjur, West Java, which has an extensive collection of other plants that have potential to be

medicinal products (Lailaty *et al.*, 2016). There are many species of *Marchantia* in the Cibodas Botanical Gardens – LIPI; one of which is *Marchantia paleacea* Bertol. As shown in Figure 1, Liverworts of the *Marchantia* genus are plants usually used in thalloid and whole plants (herbs) as medicine. Plants of this genus contain a lot of secondary metabolites, which are thought to potentially have many pharmacological activities (Fadhilla *et al.*, 2012).



Figure 1. Photo of *Marchantia paleacea* Bertol. (a species of *Marchantia*) at Cibodas Botanical Gardens – LIPI, Cianjur, West Java, Indonesia

Taxonomy classification of the genus *Marchantia*

It is classified for Plantae as a Kingdom, *Marchantiophyta* as a Division, *Marchantiopsida* (Hepaticopsida) as a Class, Marchantiales as an Order, *Marchantiaceae* as a Family, and *Marchantia* as a Genus (Raihan *et al.*, 2018). Moreover, the relationship of various liverwort taxa of the *Marchantiophyta* division is habituated to the corrected phylogeny using various biomolecular information by Long *et al.*, 2016 can be seen in Figure 2 (Bowman, 2016; Long *et al.*, 2016).

Geographic distribution

A map of the natural distribution of liverwort species can be seen in Figure 3. More than 111 to 455 liverwort species are in 10,000 km² worldwide, including Indonesia. Species abundance is also an intrinsic measure of the associated biological heterogeneity with a particular area's ecological, economic, and cultural levels (Lahlou *et al.*, 2000; Von-Konrat *et al.*, 2008)

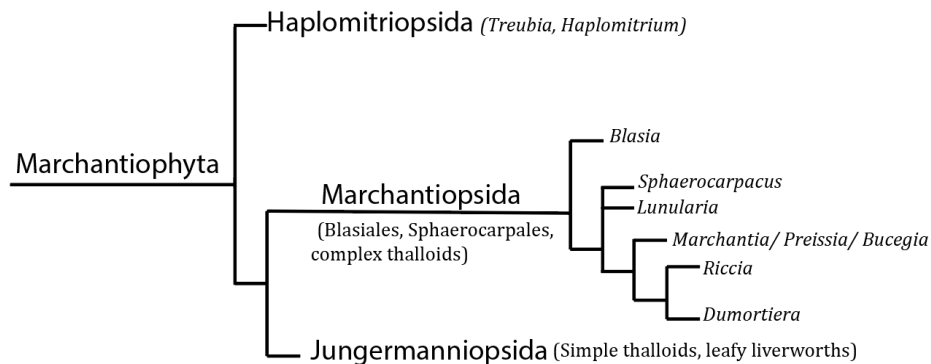


Figure 2. Relationship of various liverwort taxa (*Marchantiophyta*) habituated from the corrected phylogeny using molecular data (Long *et al.*, 2016)

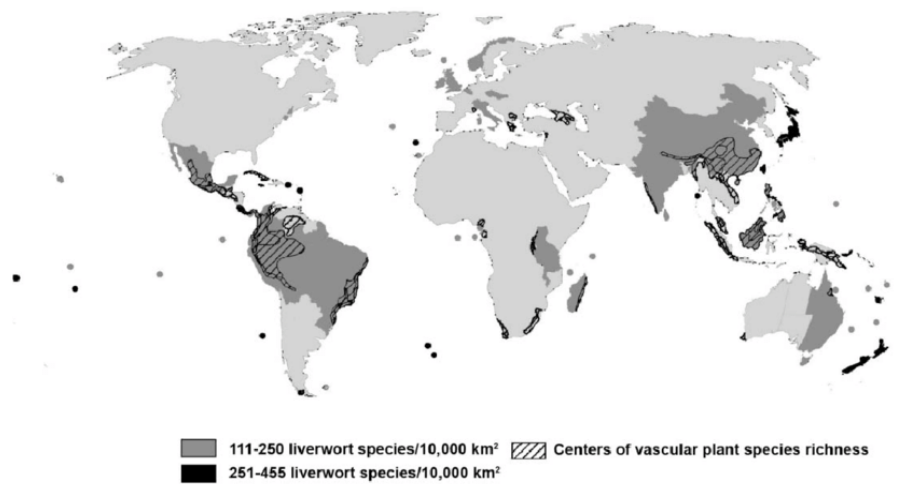


Figure 3. Natural distribution map of liverwort and vascular plant species (Von-Konrat *et al.*, 2008)

Description of botany

Species of the genus *Marchantia* have a thalloid consisting of several different layers of tissue, the topmost of which is a chlorophyll-bearing layer which is primarily a closed air space and communicates with the outside through the micro hole. Rhizoids are divided into two types, smooth and tubercular. The genital (sexual) organs in these plants are generally united in adjacent long-stemmed archegoniophores (Fadhilla et al., 2012). All these species are global and globally comprehensive in their distribution. The habitat of this species is generally found in relatively wet/ humid, shady areas and mainly found at an altitude of at least 2000 meters above sea level, such as wet open forests, riverbanks, wooden rocks, or shady rocks. The genus *Marchantia* is spread all over the world with about 65 species. Several species in Indonesia include *Marchantia emarginata* (*Marchantia palmata*), *Marchantia acaulis*, *Marchantia paleacea* Bertol. (*Marchantia nepalensis*), *Marchantia chenopoda*, *Marchantia polymorpha*, and *Marchantia geminata* Reinw. (Fadhilla et al., 2012; Heinrichs et al., 2005; N. Nurhaeni et al., 2019; Solihat and Kurnia, 2021).

RESULT

Phytochemicals and its biological activities

The results of the literature study provide several secondary metabolites from plants of the genus *Marchantia*, which have various therapeutic efficacy. The main requirements for medicinal and nutraceutical products are efficacy, safety, and quality (Ahmed et al., 2019; Altemimi et al., 2017; Rijai, 2019). The extraction process is one of the first essential steps in preparing plant test preparations. Several researchers have made considerable efforts to find an efficient extraction method to obtain the right amount of content and high efficacy. The selection of the suitable solvent is significant because if the selected solvent is not suitable,

the results obtained are minor or not obtained at all (Vishiya N, 2018; Yang et al., 2021).

Flavonoids which are one of the main constituents of *Marchantia* consist of quercetin, luteolin, apigenin, and glycosides (Cao et al., 2007). Secondary metabolite compounds from thalloid or whole plant (herb) liverwort *Marchantia polymorpha* and other *Marchantia* species are extracted with certain solvents which include: *Marchantia* A, B, D, and E, as well as Perrottetin F and Paleatin B which belong to the acyclic bis-bibenzyl group and 7',8'-dehydromarchantin A. The molecular structure of each of these compounds can be seen in Figure 4.

Marchantia A is a simple phenolic compound that is found in almost all types of *Marchantia* liverworts. *Marchantia* A and Plagiochin E (macrocyclic bis-bibenzyl) which have been isolated from the species *M. emarginata* and *M. polymorpha* have been known to have anticancer and antifungal efficacy (Asakawa, 2008; Wu et al., 2008). A study with the extraction process with ether solvent on *M. polymorpha* and with Gas chromatography-mass spectrometry/GC-MS showed the presence of several types of isoprenoid compounds as shown in Table 1 (Suire et al., 2000). The use of the Supercritical Fluid Extraction (SFE; CO₂) method and the solvent extraction process with petroleum ether on *Marchantia convoluta* produced certain essential oils. Eleven (11) compounds were identified (using GC-MS), making up 73.62% of SFE extract. The compounds 22,23-dihydro-stigmasterol (31.26%), n-hexadecanoic acid (20.35%), stigmasterol (4.55%), and octadecanoic acid (5.75%) were obtained by the previously mentioned method. For comparison, hexadecanoic acid ethyl esters (36.97%), ethyloleic (10.47%), E-11-hexadecenoic acid ethyl esters (9.77%), and linoleic acid ethyl esters (4.63%) were obtained with solvents containing petroleum ether in different literatures (Cao et al., 2007). A summary of the content of secondary metabolites obtained with certain types of solvents (or extraction processes) can be seen in Table 1.

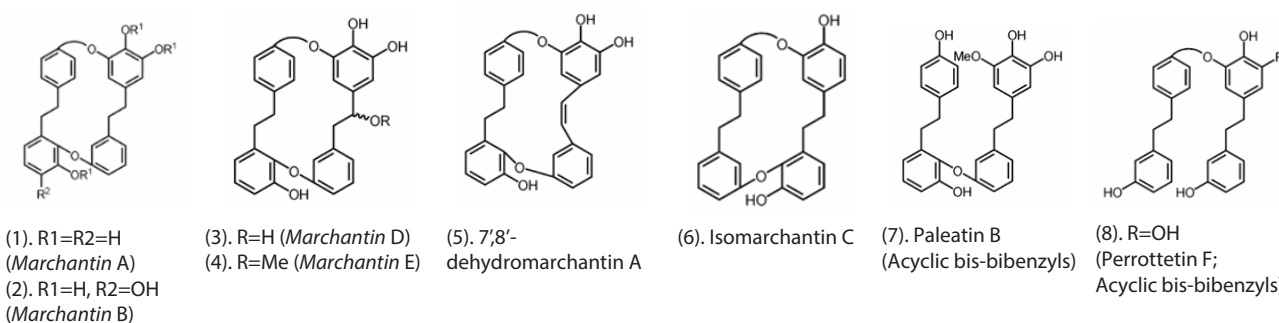


Figure 4. Secondary metabolite compounds from thalloid or whole plant (herb) liverwort *Marchantia polymorpha* and other *Marchantia* species are extracted with certain solvents which include: (1). *Marchantin* A, (2). *Marchantin* B, (3). *Marchantin* D, (4). *Marchantin* E, (5). 7',8'-dehydromarchantin A, (6). Isomarchantin C and acyclic bis-bibenzyls such as (7). Paleatin B and (8). Perrottetin F

Table 1. Content of secondary metabolites and solvent types of *Marchantia* species

Species of <i>Marchantia</i>	Secondary Metabolite Compounds	Type of Extracting Solution/Extraction Methods	Ref.
<i>Marchantia polymorpha</i>	Cyclic bis-bibenzyls; <i>Marchantin A</i> (MA); MB-G; <i>Marchantin B</i> ; <i>Marchantin D</i> ; <i>Marchantin E</i> ; Acyclic bis-bibenzyls; Perrottetin F; Paleatin B	Methanol	(Asakawa, 2008)
<i>Marchantia polymorpha</i>	Isoprenoid compounds, including thujopsene, acoradiene, β -chamigrene, cuparene, β -himachalene, γ -cuprenene, dan α -chamigren-9-one	Ether (GC-MS)	(Suire <i>et al.</i> , 2000)
<i>Marchantia paleacea</i>	<i>Marchantin A</i> (MA); <i>Marchantin B</i> ; <i>Marchantin D</i> ; <i>Marchantin E</i> ; Acyclic bis-bibenzyls such as Perrottetin F dan Paleatin B	Methanol	(Asakawa, 2007)
<i>Marchantia chenopoda</i>	<i>Marchantin A</i>	Methanol	(Asakawa, 2007)
<i>Marchantia plicata</i>	<i>Marchantin A</i>	Methanol	(Asakawa, 2007)
<i>Marchantia tosana</i>	<i>Marchantin A</i>	Methanol	(Asakawa, 2007)
Whole species of <i>Marchantia</i>	<i>Marchantin A</i> dan related to cyclic bis-bibenzyls	Ethyl Ether	(Colegate and Molyneux, 2008)
<i>Marchantia convoluta</i>	22,23-dihydro-stigmasterol (31.26%), n-hexadecanoic acid (20.35%), stigmasterol (4.55%) and octadecanoic acid (5.75%)	Supercritical (carbon dioxide) Fluid Extraction (SFE) Methods	
	Hexadecanoic acid ethyl ester (36.97%), ethyloleate (10.47%), E-11-hexadecenoic acid ethyl ester (9.77%) and linoleic acid ethyl ester (4.63%)	Petroleum Ether Extraction (PEE)	(Cao <i>et al.</i> , 2007)

DISCUSSION

Use in ethnomedicine

Mosses, especially liverworts and moss, are sources of biologically active constituents associated with pharmaceutical products. In recent years, liverworts contain many mono-, di- and lipophilic sesquiterpenoid volatile oil compounds such as bibenzyls, benzoates, cinnamates, and naphthalenes (Gahtori *and* Chatuverdi, 2011;Yayintas *and* Irkin, 2018).

Bryophytes are used in ethnopharmacological therapy in Indonesia, China, North America, India, and Greece (Fadhilla *et al.*, 2012; Sabovljevic *et al.*, 2011). Even though it is used as a traditional medicine on an

empirical basis, research in moss as a treatment is still not fully explored. There are still many opportunities for various forms of research (Mishara *et al.*, 2014). According to the existing literature, as much as 28% of it examined the exploration and medical use of mosses by North American natives, followed by China as much as 27%. Although they have long been used traditionally for medicine, the effective use of mosses in medicinal products is still minimal due to the absence of ethnomedicinal data and the lack of availability of cultivation of these materials (M. *et al.*, 2016). The ethnomedicinal use of *Marchantia* liverworts can be seen in Table 2

Table 2. The ethnomedicinal use of *Marchantia* species

Species of the <i>Marchantia</i> genus	Parts used	Medicinal uses	Countries that traditionally use the <i>Marchantia</i> genus	Ref.
<i>Marchantia polymorpha</i>	Whole plant	Treatment of liver disease, insect bites, healing external wounds, broken bones, snakebites antivenom, anti-inflammatory.	Chinese (Guangxi Zhuang autonomous district), Indonesia, India (the Khamti tribe of Lohit valley forest in eastern Arunachal Pradesh), North America (Natives), and Ancient Greek	(Asakawa, 2008; Tag <i>et al.</i> , 2007)
<i>Marchantia convoluta</i>	Whole plant	Treatment of hepatitis infection, fever symptoms, and gastric disorders.	Chinese (Guangxi Zhuang autonomous district), North America (Natives), and Ancient Greek	(Asakawa, 2008; Yayintat and Irkin, 2018)
<i>Marchantia palmate</i>	Whole plant	Treatment of acute inflammation caused by fire, heat, and skin tumors.	India (the Khamti tribe of Lohit valley forest in eastern Arunachal Pradesh), North America (Natives), and Ancient Greek	(Sabovljevic <i>et al.</i> , 2011; Tag <i>et al.</i> , 2007)
<i>Marchantia paleacea</i>	Whole plant	Reducing acute inflammation caused by various causative factors.	Chinese (Guangxi Zhuang autonomous district), North America (Natives), Indonesia, and Ancient Greek	(Sabovljevic <i>et al.</i> , 2011)

Pharmacological study

Based on searches in several scientific journals, the authors found that various parts of the liverworts of the *Marchantia* species have various pharmacological activities, which can be seen in Table 3.

• Anti-microbial and anti-fungal activity

Escherichia coli, *Proteus mirabilis* (Gram negative), and *Staphylococcus aureus* (Gram positive) which are three different types of bacteria and also *Aspergillus flavus*, *Aspergillus niger*, *Candida albicans*, and *Trychophyton mentagrophyte* which are four types of fungi were successfully tested with methanol extract. The test results showed that the test extract had efficacy against all the tested microorganisms. The best activity was shown against *Staphylococcus aureus* bacteria. The high inhibition of *Fusarium oxysporium* (76.40%) was also shown from the plant species *Marchantia polymorpha* which was extracted with methanol and flavonoid-free extracts. Further, these two extracts can perfectly inhibit the growth of *Rhizoctonia solani* (Asakawa, 2012; Mewari and Kumar, 2011).

Streptococcus viridans, *S. pyogenes*, *S. faecalis*, and *Staphylococcus aureus* which are Gram positive bacteria were tested with *Marchantin A* compound which inhibits colony propagation/ has antibacterial efficacy. *Marchantin A* was also tested against several gram-negative bacteria, namely: *Escherichia coli*, *Pseudomonas aeruginosa*, *Neisseria meningitidis*, *Pasteurella multocida*, *Haemophilus influenzae*, *Proteus mirabilis*, *Pasteurella multocida*, and *Pseudomonas aeruginosa*. The level of effectiveness of *Marchantin A* compounds against *Neisseria meningitidis* and *Haemophilus influenzae* has relatively moderate activity. The results of other research reports indicate that the symptoms of diseases caused

by Gram positive bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*) and some of the Gram negative bacteria mentioned above can be treated by *Marchantin A* (Kamory *et al.*, 1995).

Marchantia palmate was tested for potential anti-bacterial activity using five (5) different solvents against four human Gram negative pathogenic microorganisms, namely: *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae* and two microscopic Gram positive organisms *Bacillus subtilis* and *Staphylococcus aureus*. The five types in the above test were: water solvent, methanol, acetone, benzene, and petroleum-ether. Anti-bacterial activity has been demonstrated in the relatively large activity of each microorganism of this plant. The methanol extract in the anti-bacterial activity test of *Escherichia coli* has shown its efficacy, and the petroleum ether extract has the lowest efficacy against *Klebsiella pneumoniae* bacteria (Alam *et al.*, 2012). Anti-bacterial activity tests were also carried out on *Escherichia coli*, *S. Typhimurium*, *S. aureus*, and *Bacillus enteritidis* bacteria from the *Marchantia convoluta* extract (Xiao *et al.*, 2005). Significant antibacterial activity against *Acinetobacter calcoaceticus* was shown by the compound *Marchantin A* obtained from the genus *Marchantia*. Several species of the *Marchantia* genus that have been isolated and tested positive for *Marchantin A* secondary metabolites are: *Marchantia chenopoda*, *Marchantia polymorpha*, *Marchantia paleacea*, *Marchantia plicata*, and *Marchantia tosona* (Asakawa, 2007; Alam *et al.*, 2012).

Most of the anti-bacterials of plant origin are secondary metabolites of the phenolic and terpenoid groups (Fadhilla *et al.*, 2012). The anti-bacterial mechanism of phenolic compounds (e.g., *Marchantin A*) and terpenoids are to damage the cell membrane

composition and interfere with the active transport and proton forces in the bacterial cytoplasmic membrane. Furthermore, these compounds will denature and inactivate proteins such as enzymes to affect bacterial metabolism (García-Ruiz *et al.*, 2012).

Plagiochin E, a macrocyclic bis(bibenzyl) has efficacy as an antifungal isolated from *Marchantia polymorpha* L. at a dose of 16 mg/L on the formation of chitin cell walls of *C. albicans*. The process of membrane/ cell wall formation in fungi, inhibition of cell wall and septal maturation, and inhibition of shoot formation can be disrupted throughout the entire process by chitin compounds. In addition, the process of division and growth of fungal cells can also be inhibited by chitin compounds (Wu *et al.*, 2008). Wu *et al.* (2009) also described that when *Candida albicans* was exposed to *Plagiochin E*, there was a decrease in mitochondrial ATP levels due to an inhibitory effect on mitochondrial dehydrogenase activity and an increase in mitochondrial F0F1-ATPase. Thus, this suggests the procedure of antifungal action of *Plagiochin E* (Wu *et al.*, 2009). The process of cell death (apoptosis) in the fungus *Candida albicans* begins through the metacaspase pathway (Wu *et al.*, 2009). Sun *et al.* (2009) provided a detailed description on *Candida albicans* related to the antifungal activity of *Plagiochin E* with fluconazole compounds. The results showed that *Plagiochin E* increased the antifungal activity of fluconazole by interfering with the ergosterol biosynthetic instrument.

Aspergillus versicolor, *Trichoderma viride*, *Penicillium funiculosum*, *Aspergillus fumigatus*, and *Penicillium ochrochloron* are five fungal species tested for colony growth inhibition by *Marchantia polymorpha* extract. The results showed anti-fungal activity against the five fungal species. From other research conducted in vitro, *Marchantia polymorpha* activity showed better antifungal activity than some extracts from other species of plant simplicia (Sabovljevic *et al.*, 2011).

Methanol and chloroform extracts from *Marchantia polymorpha* have been tested for anti-fungal and potential to inhibit bacterial growth against Gram negative bacteria (*Xanthomonas oryzae*, *Pasturella multocida*) and several types of fungi (*Fusarium oxysporum*, and *Sclerotium rolfsii*). The two extracts showed consequential anti-bacterial activity against *Xanthomonas oryzae* and *Pasturella multocida* and anti-fungal against fungal species *Sclerotium rolfsii* and *Fusarium oxysporum*. So these results show great potential for *Marchantia polymorpha* to be developed in broad-spectrum anti-microbial formulations in the future (Gahtori and Chatuverdi, 2011).

• Antioxidant activity

Plant species of the genus *Marchantia* are prosperous sources of herbal antioxidant substances such as flavonoids, tannins, and phenolics which play a major part as antioxidant agents, thus make the plants as free radical scavenger properties. *Marchantia*

polymorpha for DPPH radical scavenger and antioxidant activity of ABTS has shown the IC50 value in the methanol extract of *Marchantia polymorpha* is 0.4495 ± 0.029 mg/mL, and the extract of ethyl acetate is 0.2756 ± 0.01 mg/mL. Meanwhile, the results of ABTS antioxidant activity showed the IC50 value of the *Marchantia polymorpha* methanol extract of 0.2441 ± 0.009 mg/mL and the ethyl acetate extract of 0.2126 ± 0.01 mg/mL. This examination determined the free radical scavenger/ antioxidant activity of *Marchantia polymorpha*. The methanolic extract of thalloid *Marchantia polymorpha* produces luteolin compounds which are polyphenolic compounds. In addition, from the thallus of this species, other phenolic compounds were obtained, namely: gallate, vanillate, chlorogenic, cinnamic, protocatechol, coumarate, ferulate, sinapic, caffeate, and hydroxyl benzoate which have close associations with antioxidant activity (Gokbulut *et al.*, 2012).

• Muscle relaxant activity

There is a structural relationship between the relaxant pharmacological activity of *Marchantin A* and cyclic bis-bibenzyls with the alkaloid tubocurarine. Most astoundingly, *Marchantin A* and trimethyl ether of *Marchantin A* also exhibited muscular relaxant activity. Trimethyl ether of *Marchantin A* compound at a concentration of 2×10^{-7} – 2×10^{-4} M in Ringer's solution added with nicotine (10^{-5} – 10^{-4} M) increased the efficacy of muscle relaxants. In addition to frogs, *Marchantin A* and its trimethyl ether also had muscular relaxant activity in-vivo (mice). The mechanism of action of *Marchantin A* and its trimethyl ether is still unknown (Asakawa, 2008; Colegate and Molyneux, 2008).

• Cathepsin L dan B inhibitor activity

Marchantin compound has *Cathepsin L* and *B* inhibitory activity that correlates with osteoporosis (Katsunuma, 1997) and allergies (Matsunaga *et al.*, 1993). *Marchantin* is a natural chemopreventive compound that has inhibitory activity on the enzyme. Isomarchantin C had the most potent inhibitory effect on each of these enzymes (95% for *Cathepsin L* and 93% for *Cathepsin B* at 10^{-5} M).

• Cardiotoxic activity

Marchantin A exhibits cardiotoxic activity that increases coronary blood flow by 2.5 mL/min at 0.1 mg dose (Asakawa, 2007).

• Anti-inflammatory activity

Marchantia palmata is used in treating acute inflammation caused by fire or hot water. *M. polymorpha* relieves pain due to acne on the face or other body, which uses the same as *M. palmate*. There was research related to the use of albumin denaturation inhibition method as an anti-inflammatory activity test method that was carried out on the ethanol extract of *M. polymorpha*. The albumin synthesis process was

inhibited by *M. polymorpha* extract which depended on the extract dose. Therefore, the anti-inflammatory activity produced was comparable to the anti-inflammatory activity of the drug compound sodium diclofenac (Tag *et al.*, 2007).

• Cytotoxic (anti-cancer) activity

Three types of extracts from the *Marchantia convoluta* plant, namely petroleum ether, ethyl acetate and n-butanol were then tested for their cytotoxic activity against human lung carcinoma cells (H1299) and relatively small liver carcinoma cells (HepG2). Cytotoxic activity and cell viability were significant in ethyl acetate extract compared to other extracts against lung and liver carcinoma cells (Lahlou *et al.*, 2000). *Marchantia polymorpha*, showed anti-cancer activity against human nasopharyngeal carcinoma (Jensen *et al.*, 2012). *Marchantia paleacea*, *Marchantia polymorpha*, and *Marchantia tosana* produced *Marchantin A* compounds that have shown cytotoxic activity against leukemia cells (Asakawa, 2007). *Marchantin A* was obtained from the species *M. polymorpha* in Iceland, and it was found that *Marchantin A* promoted decreased cell viability of breast cancer cell lines A256, MCF7, and T47D. Fluorescence microscopy confirmed the antimicrotubular effect of *Marchantin A* (Jensen *et al.*, 2012).

• Hepatoprotective activity

In *Marchantia convoluta* simplicia, research has been carried out to protect the liver and treat skin swelling ethnomedicinally in China. Xiao (2005) has examined the pharmacological activity of the secondary metabolites of the flavonoid *Marchantia convoluta*. High doses of *M. convoluta* (40 g/mL) succeeded in reducing the activity of SGPT/ALT and SGOT/AST enzymes in the blood serum of rats with acute hepar injury caused by CCl₄ and improving the total protein (TP) and alkaline phosphatase (ALP) content (Fernando and Soysa, 2014; Jian-Bo *et al.*, 2005; Karmakar *et al.*, 2020; Purkon *et al.*, 2021b).

• Other therapeutic effects

M. polymorpha is used as an antipyretic activity, hepatoprotector, antidote and antivenom for snakebite, diuretic, and used to heal wounds, fractures, burns and open wounds (Asakawa, 2008). Liverworts such as *M. tosana* exhibit antifungal, antimicrobial, and antitumor activity (Lahlou *et al.*, 2000). *M. paleacea* has been used as an antibacterial against pathogenic bacteria and food spoilers in Indonesia (Fadhilla *et al.*, 2012).

Table 3. Summary of *Marchantia* species and their biological activity (pharmacological activities)

Species of the <i>Marchantia</i> genus	Parts used	Dose concentration	Extract	Medicinal uses	Ref.
<i>Marchantia polymorpha</i>	Thalloid	5.30-23.7 µg/mL	Methanol	Anti-HIV-1 activity (for the <i>Marchantin A</i> , B, D, paleatin B and perrottetin F compounds).	(Asakawa, 2007)
	Thalloid	14.4-97.5 µM	Methanol	DNA polymelase β inhibitory (ID50) (for the <i>Marchantin A</i> , B, D, paleatin B, and perrottetin F compounds).	(Asakawa, 2007)
	Thalloid	3.7-20 µM	Methanol	Cytotoxic (against KB cell and P-388) (for the <i>Marchantin A</i> , B, D, paleatin B and perrottetin F compounds).	(Asakawa, 2007)
	Whole plant	n/a	Methanol	Antipyretic, hepatoprotective, antidote, diuretic activity, used to heal cuts, fractures, antivenom for snake bites, burns, and open wounds.	(Asakawa, 2008)
<i>M. polymorpha</i> , <i>M. paleacea</i> , <i>M. chenopoda</i> , <i>M. plicata</i> and <i>M. tosana</i> containing <i>Marchantin A</i>	Thalloid	Dose concentration data are listed respectively in the test results column	Methanol	Anti-bacterial activity against <i>Acinetobacter calcoaceticus</i> (6.25 µg/mL), <i>Alcaligenes faecalis</i> (100 µg/mL), <i>Bacillus cereus</i> (12.5 µg/mL), <i>Bacillus megaterium</i> (25 µg/mL), <i>Bacillus subtilis</i> (25 µg/mL), <i>Cryptococcus neoformans</i> (12.5 µg/mL), <i>Enterobacter cloacae</i> (100 µg/mL), <i>Escherichia coli</i> (100 µg/mL), <i>Proteus mirabilis</i> (100 µg/mL), <i>Pseudomonas aeruginosa</i> (100 µg/mL), <i>Salmonella typhimurium</i> (100 µg/mL), <i>Staphylococcus aureus</i> (3.13-25 µg/mL).	(Asakawa, 2007)

The continuation of Table 3

Species of the <i>Marchantia</i> genus	Parts used	Dose concentration	Extract	Medicinal uses	Ref.
<i>M. polymorpha</i> , <i>M. paleacea</i> , <i>M. chenopoda</i> , <i>M. plicata</i> and <i>M. tosana</i> containing <i>Marchantin A</i>	Thalloid	Dose concentration data are listed respectively in the test results column	Methanol	Anti-fungal activity against <i>Alternaria kikuchiana</i> (MIC 100 µg/mL), <i>Aspergillus fumigatus</i> (MIC 100 µg/mL), <i>Aspergillus niger</i> (25-100 µg/mL), <i>Candida albicans</i> , <i>Mirospororum gypseum</i> , <i>Penicillium chrysogenum</i> (100 µg/mL), <i>Piricularia oryzae</i> (12.5 µg/mL), <i>Rhizoctonia solani</i> (50 µg/mL), <i>Saccharomyces cerevisiae</i> , <i>Sporothrix schenckii</i> (100 µg/mL) and the dermatophytes <i>Trichophyton mentagrophytes</i> (3.13 µg/mL) and <i>Trichophyton rubrum</i> (100 µg/mL).	(Asakawa, 2007)
<i>Marchantia polymorpha</i> L.	Thalloid	Dose concentration data are listed respectively in the test results column	Methanol and Chloroform	Anti-bacterial activity (Gram negative) against <i>Xanthomonas oryzae</i> [11.58% Inhibition; 2.50 µg/mL (MIC) & 2.75 µg/mL (MBC)], <i>Pasturella multocida</i> (12.55% inhibition; 1.25 µg/mL (MIC) & 1.25 µg/mL (MBC)]	(Gahtori and Chatuverdi, 2011)
<i>Marchantia polymorpha</i> L.	Thalloid	Dose concentration data are listed respectively in the test results column	Methanol and Chloroform	Anti-fungal activity against <i>Sclerotium rolfisii</i> (32.65% inhibition; 4.50 µg/mL) and <i>Fusarium oxysporum</i> (33.44% inhibition; 0.65 µg/mL)	(Gahtori and Chatuverdi, 2011)
Species of <i>Marchantia</i> containing <i>Marchantin D</i> and <i>E</i>	Whole plant	ID50 2.0-95.0 g/mL	Methanol	Calmodulin Inhibitory Activity	(Asakawa, 2007)
		76-84% on 10 ⁻⁶ mol	Methanol	5-lipoxygenase inhibitory Activity	
Species from <i>Marchantia</i> contain phenolic compounds (<i>bis-bibenzylys</i> group)	Whole plant	Dose concentration data are listed respectively in the test results column	Methanol	<i>Cyclooxygenase</i> inhibitory activity: <i>Marchantin A</i> (IC ₅₀ 46.4 µM); <i>Marchantin B</i> (55.9 µM) and <i>Marchantin E</i> (58.0 µM)	(Asakawa, 2008)
Species from <i>Marchantia</i> containing <i>Marchantin A</i> and related cyclic <i>bis-bibenzylys</i>	Whole plant	2 x10 ⁻⁷ to 2 x 10 ⁻⁴ M in ringer solution	Ethyl Ether	Muscle relaxing activity (in-vitro and in-vivo test in mice)	(Asakawa, 2008; Colegate and Molyneux, 2008)
Species from <i>Marchantia</i> containing <i>Isomarchantin C</i>	Whole plant	95% for <i>cathepsin</i> L and 93% for <i>cathepsin</i> B at 10 ⁻⁵ M	Methanol	Cathepsin L and B inhibitory activity	Katsunuma, 1997; (Asakawa, 2007)
Species of <i>Marchantia</i> containing <i>Marchantin A</i>	Whole plant	0.1 mg dose (increase coronary blood flow 2.5 mL/min)	Methanol	Cardiotonic activity	(Asakawa, 2007)
<i>Marchantia polymorpha</i>	Whole plant	Plagiochin E at a dose of 16 mg/L	n/a	Antifungal against <i>Candida albicans</i>	(Wu <i>et al.</i> , 2008)

CONCLUSION

Natural resources, especially the *Marchantia* species of liverworts, are still considered potential candidates for discovering and developing preventive, promotive, rehabilitative, and curative medicinal products. The content of secondary metabolites that are already known from this genus and have the potential to become medicinal/ nutraceutical products are: *Marchantia* A, B, D and E; *Isomachantin* C; *Plagiochin* E; *Paleatin* B and *Perrottetin* F. The pharmacological activities obtained were also quite a lot which included: anti-bacterial, antifungal, antioxidant, cytotoxic activity (anti-cancer), anti-inflammatory, cardiotoxic activity, muscle relaxant activity, hepatoprotector, the inhibitory activity of *Cathepsin* L and B (antiosteoporosis). Medicinal/ nutraceutical products with these functions can be formulated in certain dosage forms, such as functional foods, supplements, and traditional medicinal products. Some researchers believe that bioactive phytochemicals are responsible for the actions of these various pharmacological activities. More work is needed to isolate other active substances, *in-vivo* preclinical testing for the results of studies that have only reached *in-vitro* tests and clinical trials of secondary metabolites with therapeutic effects from this *Marchanti* species.

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