Chemical Diversity of Liverworts From *Frullania* Genus

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Abstract

*Frullania* is one of the largest and taxonomically most complex genus of leafy liverworts. Current morphology-based estimates of *Frullania* diversity are close to 400 species; however, species level-classification of *Frullania* has been regarded notoriously difficult and subject to many studies. The liverworts classified in this genus have been studied using morphological evidence and molecular markers but also in terms of secondary metabolite composition. Up to now 98 *Frullania* species have been chemically investigated. As a result, it is known that *Frullania* species are characterized by a remarkable chemical diversity. The most characteristic compounds present in this liverwort genus are sesquiterpene lactones with eudesmanolides as the most diverse group, and aromatic compounds belonging to bibenzyls. In this review paper we report the distribution of secondary metabolites in all chemically investigated *Frullania* species and discuss some aspects concerning the division of this genus into chemotypes.

Keywords

*Frullania*, liverworts, sesquiterpene lactones, eudesmanolides, bibenzyls, chemotypes

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*Frullania* Raddi is a genus of leafy liverworts and is characterized by its often reddish pigmentation and includes both narrow endemics and nearly cosmopolitan species. This liverwort genus has a worldwide distribution with centers of diversity in the humid tropics and warm temperate regions. Many species of *Frullania* occur not only in moist but also in rather dry vegetation.¹² *Frullania* is also the largest and taxonomically most complex liverwort genus classified in order Porellales within family Frullaniaceae.³⁴

Species of liverworts have traditionally been circumscribed using morphological evidence. It was the time that geographical or typological species concepts was preferred and liverwort species were regarded as largely invariable units with small ranges. Then, the intraspecific morphological variation concept was accepted, and it contributed to the reduction of local binomials to synonyms of widespread liverwort species.⁴⁵ More recently, morphology-based species concepts have been tested using evidence from molecular markers including isozymes, and variable regions of the nuclear and the plastid genomes,²⁶ as well as secondary metabolites.⁷⁸

In case of *Frullania* there are estimated 300-375 species,⁹ however, species level-classification of *Frullania* has been regarded notoriously difficult and subject to much controversy.¹ They have been various proposals for a subdivision of *Frullania* into natural species groups.¹⁰¹¹ As a result, more than 15 subgenera and over 30 sections and subsections based on morphology were established.¹¹ Recently, Hentschel et al. (2009)⁶ presented the most comprehensive molecular phylogeny of *Frullania* to date. The liverworts classified in genus *Frullania* have not only been studied using morphological evidence and molecular markers but also in terms of secondary metabolite composition.¹²¹⁶ The use of the secondary metabolites as aids to plant taxonomy was popularized by the publication of Swain (1963).¹³ Terpenoids not only sesquiterpene lactones,¹⁸¹⁹ but also flavonoids²⁰ are of value in the taxonomic and evolutionary investigations of plants. In this review paper we report the distribution of secondary metabolites in all chemically investigated *Frullania* species and discuss some aspects concerning the division of this genus into chemotypes.

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Table 1. Group of Compounds Found in Chemically Investigated *Frullania* Species.

| No. | *Frullania* species       | Collection place                      | Group of compounds                                                                                      | References               |
|-----|---------------------------|---------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------|
| 1   | *Frullania africana*      | Herbarium sample                      | Flavonoids                                                                                             | Yuzawa et al., 1987 23  |
|     |                           |                                       |                                                                                                         | Asakawa 1995 22          |
| 2   | *Frullania amplicipitans* | Miyazaki, Japan; Miyake Island, Japan | Sesquiterpene hydrocarbons; Diterpenes; Bibenzyls                                                       | Asakawa et al., 1981 12 |
| 3   | *Frullania anomala*       | South Island, New Zealand             | Sesquiterpene hydrocarbons; Bibenzyls; Lipids                                                           | Asakawa et al., 2003 14 |
| 4   | *Frullania apiculata*     | Cameron Highlands, Pahang, Malaysia   | Sesquiterpene lactones                                                                                   | Asakawa et al., 1983 24 |
| 5   | *Frullania aroeae*        | Colombia, South America                | Flavonoids                                                                                             | Kraut et al., 1995 13   |
| 6   | *Frullania asagayama*     | Pounds Escarpment, Illinois, USA      | Sesquiterpene lactones                                                                                   | Asakawa et al., 1991 25 |
| 7   | *Frullania aterrima*      | North Island, New Zealand             | Sesquiterpene hydrocarbons and lactones; Diterpenes                                                    | Asakawa et al., 2003 14 |
| 8   | *Frullania aterrima* var. | North Island, New Zealand             | Sesquiterpene hydrocarbons and lactones                                                                 | Asakawa et al., 2003 14 |
| 9   | *Frullania bella*         | Proney village and Yate lake, New Caledonia | Sesquiterpene hydrocarbons; Oxygenated sesquiterpenes                                           | Météoy et al., 2016 26  |
| 10  | *Frullania brachyclada*   | Herbarium sample                      | Flavonoids                                                                                             | Yuzawa et al., 1987 23  |
| 11  | *Frullania bicornistipula*| Panama                                | Sesquiterpene hydrocarbons and lactones                                                                 | Asakawa 1995 22          |
| 12  | *Frullania bonica*        | Hahajima Island, Japan                | Bibenzyls                                                                                              | Asakawa et al., 1981 12 |
| 13  | *Frullania brasiliensis*  | Tucuman province, Argentina; Loja province, Ecuador | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Sterols; Triterpenes; Bibenzyls; Other aromatic compounds | Asakawa 1995 22 |
|     |                           |                                       |                                                                                                         | Bardon et al., 2002 27  |
|     |                           |                                       |                                                                                                         | Valarezo et al., 2020 26 |
| 14  | *Frullania brotheri*      | Wakayama Prefecture, Japan            | Sesquiterpene lactones                                                                                   | Takeda et al., 1983 29  |
| 15  | *Frullania californica*   | Eugene, Oregon, USA                   | Sesquiterpene lactones                                                                                   | Asakawa et al., 1991 25 |
| 16  | *Frullania cesatiana*     | Switzerland: Tessin; Italy: South Tirol | Flavonoids                                                                                             | Kraut et al., 1995 13   |
| 17  | *Frullania chesadieri*    | North Island, New Zealand             | Sesquiterpene hydrocarbons and lactones; Lipids                                                         | Asakawa et al., 2003 14 |
| 18  | *Frullania clavata*       | Blue Mountains, New South Wales, Australia | Sesquiterpene hydrocarbons; Oxygenated sesquiterpenes                                            | Asakawa et al., 1983 24 |
| 19  | *Frullania confertihyla*  | Herbarium sample                      | Sesquiterpene hydrocarbons and lactones                                                                 | Yuzawa et al., 1987 23  |
| 20  | *Frullania congesta*      | Stewart Island, New Zealand           | Sesquiterpene hydrocarbons and lactones                                                                 | Asakawa et al., 2003 14 |
| 21  | *Frullania concinuta*     | Paramo el Angel, Ecuador              | Sesquiterpene lactones; Bibenzyls; Bisbibenzyls                                                         | Flégel et al., 1999 30  |
| 22  | *Frullania cornuta*       | Koghis forest, New Caledonia          | Sesquiterpene hydrocarbons; Oxygenated sesquiterpenes                                                   | Météoy et al., 2010 26  |
| 23  | *Frullania davurica*      | Tokushima, Japan; Hokkaido, Japan     | Monoterpenes; Sesquiterpene hydrocarbons and lactones; Bibenzyls; Flavonoids; Sterols | Mues et al., 1984 41    |
|     |                           | Tottori, Japan                        |                                                                                                         | Asakawa 1995 22          |
| 24  | *Frullania densiloba*     | Tokushima, Japan                      | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes                                     | Asakawa et al., 1980 32 |
|     |                           |                                        |                                                                                                         | Asakawa et al., 1981 12 |
| 25  | *Frullania deplanata*     | Tasmania, Australia; North Island, New Zealand | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes                                     | Asakawa et al., 2003 14 |
| 26  | *Frullania dilatata*      | Dordogne, France                      | Monoterpenes; Sesquiterpene hydrocarbons and lactones                                                 | Asakawa et al., 1980 32 |
|     |                           |                                        |                                                                                                         | Asakawa et al., 1981 12 |
|     |                           |                                        |                                                                                                         | Asakawa 1982 28          |
| 27  | *Frullania dilatata* var. | Black Sea, near Varna, Bulgaria       | Monoterpenes; Sesquiterpene hydrocarbons and lactones                                                 | Asakawa et al., 1980 32 |
|     | anomala                   |                                        |                                                                                                         | Asakawa et al., 1981 12 |
|     |                           |                                        |                                                                                                         | Nagashima et al., 1994 33 |
| 28  | *Frullania diversitexta*  | Miyazaki, Japan                       | Monoterpenes; Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes                       | Asakawa et al., 1980 32 |
|     |                           |                                        |                                                                                                         | Asakawa et al., 1981 12 |

(Continued)
| No. | Frullania species                  | Collection place                                      | Group of compounds                                                                                     | References                                      |
|-----|----------------------------------|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------|------------------------------------------------|
| 29  | *Frullania eboracensis*          | New York, Adirondack Mts. and Rensselaer county; New Jersey, Warren county, USA | Flavonoids; Aromatic compounds                                                                       | Kraut et al., 1995<sup>13</sup> |
| 30  | *Frullania ecklonii*             | Herbarium sample                                      | Flavonoids                                                                                             | Yuzawa et al., 1987<sup>23</sup>               |
| 31  | *Frullania ericoides*            | Kochi, Japan                                           | Sesquiterpene hydrocarbons; Bibenzyls; Flavonoids                                                     | Asakawa et al., 1981<sup>34</sup>              |
|     |                                  | Tokushima, Japan                                      |                                                                                                         | Asakawa et al., 1983<sup>34</sup>              |
|     |                                  | Noumea, New Caledonia                                  |                                                                                                         | Métoyer et al., 2016<sup>26</sup>              |
| 32  | *Frullania falsiloba*            | Blue Mountains, New South Wales, Australia              | Monoterpenes; Sesquiterpene hydrocarbons; Oxygenated sesquiterpenes; Diterpenes, Sterols, Bibenzyls, Other aromatic compounds; Lipids | Asakawa et al., 1983<sup>34</sup>              |
|     |                                  | North Island, New Zealand                              |                                                                                                         | Asakawa et al., 2003<sup>34</sup>              |
|     |                                  |                                                        |                                                                                                         | Nagashima et al., 2006<sup>35</sup>            |
| 33  | *Frullania falcicornuta*         | Koghis forest, New Caledonia                          | Sesquiterpene hydrocarbons; Oxygenated sesquiterpenes                                                   | Métoyer et al., 2016<sup>26</sup>              |
| 34  | *Frullania fragilifolia*         | Haut-Rhin, France                                      | Monoterpenes; Sesquiterpene hydrocarbons                                                                | Asakawa et al., 1980<sup>36</sup>              |
|     |                                  |                                                        |                                                                                                         | Asakawa et al., 1981<sup>32</sup>              |
| 35  | *Frullania franciscana*          | Ecola State Park, Cannon Beach, Oregon, USA           | Sesquiterpene lactones                                                                                  | Sass 1981<sup>12</sup>                         |
| 36  | *Frullania fugax*                | North Island, New Zealand                              | Sesquiterpene hydrocarbons, Diterpenes; Sterols; Aromatic compounds                                   | Asakawa et al., 2003<sup>34</sup>              |
| 37  | *Frullania gandichandii*         | Kalimantan Timur, Borneo                               | Sesquiterpene hydrocarbons; Oxygenated sesquiterpenes                                                   | Asakawa et al., 1983<sup>24</sup>              |
| 38  | *Frullania gibosa*               | Herbarium sample                                      | Flavonoids                                                                                             | Kraut et al., 1995<sup>13</sup>               |
| 39  | *Frullania grastinii*            | Galapagos Island, Ecuador                              | Flavonoids                                                                                             | Yuzawa et al., 1987<sup>23</sup>               |
| 40  | *Frullania hamatiloba*           | Tokushima, Japan                                       | Monoterpenes; Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Diterpenes; Flavonoids; Sterols | Toyota et al., 1988<sup>38</sup>               |
|     |                                  | Shanxi Province, China                                 |                                                                                                         | Hashimoto et al., 1998<sup>39</sup>            |
|     |                                  |                                                        |                                                                                                         | Qiao et al., 2019<sup>40</sup>                 |
| 41  | *Frullania incumbens*            | North Island, New Zealand                              | Sesquiterpene hydrocarbons and lactones; Diterpenes; Bibenzyls; Lipids                                | Asakawa et al., 1996<sup>41</sup>              |
|     |                                  |                                                        |                                                                                                         | Asakawa et al., 2003<sup>14</sup>              |
| 42  | *Frullania inflata*              | Mie, Japan                                             | Sesquiterpene hydrocarbons and lactones                                                                | Asakawa et al., 1980<sup>32</sup>              |
|     |                                  |                                                        |                                                                                                         | Asakawa et al., 1981<sup>12</sup>              |
| 43  | *Frullania inflata var. mogybarae*| Herbarium sample                                      | Monoterpenes                                                                                           | Asakawa et al., 1981<sup>34</sup>              |
| 44  | *Frullania inouei*               | Yunnan Province, China                                 | Diterpenes; Bibenzyls                                                                                  | Guo et al., 2010<sup>42</sup>                  |
| 45  | *Frullania jackii*               | Herbarium sample                                      | Sesquiterpene hydrocarbons; Sterols, Bibenzyls, Flavonoids                                            | Mues et al., 1984<sup>31</sup>                 |
| 46  | *Frullania kagoshimensis*        | Miyazaki, Japan                                        | Sesquiterpene hydrocarbons                                                                             | Asakawa et al., 1995<sup>32</sup>              |
| 47  | *Frullania lasiothra*            | Herbarium sample                                      | Flavonoids                                                                                             | Yuzawa et al., 1987<sup>23</sup>               |
| 48  | *Frullania lobulata*             | Brunswick Peninsula, Chile                             | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Lipids                            | Asakawa et al., 2003<sup>34</sup>              |
| 49  | *Frullania magellanica*          | Bahia Buen Suceso, Argentine                           | Sesquiterpene hydrocarbons and lactones; Lipids                                                       | Asakawa et al., 2003<sup>34</sup>              |
| 50  | *Frullania mamiillilosa*         | Creek Pernod and Prony village, New Caledonia          | Sesquiterpene hydrocarbons and lactones                                                               | Métoyer et al., 2016<sup>26</sup>              |
| 51  | *Frullania media*                | Stewart Island, New Zealand                            | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Diterpenes | Asakawa et al., 2003<sup>14</sup>              |
| 52  | *Frullania microaestivus*        | Prov. Magallanes, Chile                                | Aromatic compounds                                                                                     | Asakawa et al., 2003<sup>14</sup>              |
| 53  | *Frullania monogena*             | Mie, Japan                                             | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Diterpenes; Bibenzyls                | Asakawa et al., 1981<sup>12</sup>              |
| 54  | *Frullania monoyama*             | Miyazaki, Japan                                        | Sesquiterpene hydrocarbons                                                                             | Asakawa et al., 1980<sup>32</sup>              |
|     |                                  | Mie, Japan                                             |                                                                                                         | Asakawa et al., 1981<sup>12</sup>              |
| 55  | *Frullania multilocera*          | Koghis forest, New Caledonia                          | Sesquiterpene hydrocarbons                                                                             | Métoyer et al., 2016<sup>26</sup>              |

(Continued)
| No. | Frullania species               | Collection place          | Group of compounds                                      | References |
|-----|--------------------------------|---------------------------|---------------------------------------------------------|------------|
| 56  | Frullania musciola (Frullania brittoniae spp. truncatifolia) | Miyazaki, Japan; Hiroshima, Japan; Shandong Province, China; Ilha Terceira, Azores | Sesquiterpene lactones; Flavonoids; Bibenzyls; Phthalides; Other aromatic compounds | Asakawa et al., 1976; Asakawa et al., 1981; Kraut et al., 1993; Kraut et al., 1994; Lou et al., 2002 |
| 57  | Frullania nepalensis           | Arishan, Taiwan           | Sesquiterpene lactones; Oxygenated sesquiterpenes;      | Tori et al., 1990; Asakawa et al., 1991; Asakawa 1995 |
| 58  | Frullania insignisensis        | Oregon, USA               | Sesquiterpene lactones; Aromatic compounds              | Asakawa et al., 1991; Kim et al., 1996 |
| 59  | Frullania obscura              | Herbarium sample          | Flavonoids                                              | Yuzawa et al., 1987 |
| 60  | Frullania ossumiensis          | Miyazaki, Japan           | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Bibenzyls | Asakawa et al., 1980; Asakawa et al., 1981 |
| 61  | Frullania orientalis           | Herbarium sample          | Flavonoids                                              | Yuzawa et al., 1987 |
| 62  | Frullania parvispina           | Kyoto, Japan              | Sesquiterpene hydrocarbons and lactones; Bibenzyls      | Asakawa et al., 1981; Asakawa et al., 1981 |
| 63  | Frullania patula               | North Island, New Zealand | Sesquiterpene hydrocarbons; Diterpenes; Bibenzyls       | Asakawa et al., 2003 |
| 64  | Frullania prusilhata           | Tokushima, Japan; Miyazaki, Japan | Monoterpenes; Sesquiterpene hydrocarbons; Bibenzyls | Asakawa et al., 1979; Asakawa et al., 1981 |
| 65  | Frullania planicarinata        | Herbarium sample          | Flavonoids                                              | Yuzawa et al., 1987 |
| 66  | Frullania polysticta           | Madeira                   | Flavonoids                                              | Kraut et al., 1993 |
| 67  | Frullania probochophora        | Tasmania, Australia; South Island, New Zealand | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Aromatic compounds | Asakawa et al., 2003 |
| 68  | Frullania pychanthha           | Stewart Island, New Zealand | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Bibenzyls | Asakawa et al., 2003 |
| 69  | Frullania pyrnantha            | North Island and Stewart Island, New Zealand | Monoterpenes; Sesquiterpene hydrocarbons; Diterpenes; Bibenzyls; Lipids | Asakawa et al., 2003 |
| 70  | Frullania ramuligera           | Miyazaki, Japan           | Sesquiterpene hydrocarbons and lactones                 | Asakawa et al., 1980; Asakawa et al., 1981 |
| 71  | Frullania riganeirensis        | Colombia, South America   | Flavonoids                                              | Yuzawa et al., 1987 |
| 72  | Frullania rostrata             | Stewart Island, New Zealand | Sesquiterpene lactones                                | Asakawa et al., 2003 |
| 73  | Frullania scalaris             | Yate lake, New Caledonia  | Sesquiterpene hydrocarbons and lactones                 | Métoyer et al., 2016 |
| 74  | Frullania scadens              | North Island, New Zealand | Sesquiterpene hydrocarbons; Bibenzyls; Lipids           | Asakawa et al., 2003 |
| 75  | Frullania serrata              | Cameron Highlands, Pahang, Malaysia Yunnan Province, China | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Bibenzyls | Asakawa et al., 1983; Asakawa et al., 1991; Li et al., 2014 |
| 76  | Frullania solanderiana         | North Island, New Zealand | Sesquiterpene hydrocarbons; Lipids                      | Asakawa et al., 2003 |
| 77  | Frullania spinifera            | North Island, New Zealand | Monoterpenes; Sesquiterpene hydrocarbons; Bibenzyls; Lipids | Asakawa et al., 2003 |
| 78  | Frullania sphaerocephala       | Herbarium sample          | Sesquiterpene hydrocarbons and lactones; Flavonoids     | Asakawa 1995; Yuzawa et al., 1987 |
| 79  | Frullania squamissula          | North Island, New Zealand | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Diterpenes, Triterpenes, Aromatic compounds | Asakawa et al., 2003; Asakawa et al., 2008 |
| 80  | Frullania tamariscii            | Dordogne, France; Jura, France; Corsica, France | Monoterpenes; Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes | Asakawa et al., 1979; Asakawa et al., 1980; Asakawa 1995; Asakawa et al., 2013; Pannequin et al., 2017 |
One of the outstanding features of the liverworts is their chemistry. They produce a wide array of secondary metabolites, and up to now over several hundred new terpenoids, and aromatic compounds including bibenzyls and bisbibenzyls with more than 40 new carbon skeletons have been isolated. As a result of phytochemical studies, *Frullania* species are now known to produce a wide array of secondary metabolites. As shown in Table 1, 98 *Frullania* species have been chemically investigated. Most of the compounds either detected in or isolated from these species are terpenoids, aromatic compounds, and flavonoids. Among terpenoids, the sesquiterpenes are the most diverse group, but the presence of mono-, di-, and triterpenes was also confirmed. α-Pinene (1), β-pinene (2), camphene (3), δ-phellandrene (4), myrcene (5), limonene (6), and α-terpinene (7) are the monoterpenoids frequently found in *Frullania* species (Figure 1). Due to the fact that most of the *Frullania* species elaborate the same monoterpenoids, it is difficult to use them as chemosystematic markers.

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In comparison to monoterpenoids, the sesquiterpenoids present in this liverwort genus are characterized by a wide range of different sesquiterpene skeletons. There are especially eudesmanes, elemenides, eremophilanes, germacranes, bazzananes, pacifigor-ganes, and other minor groups of sesquiterpenoids, like aromadendranes, africanes, barbaranes, cadinanes, cuparanes, ditaranes, farnesanes, guainanes, monocyclofarnesanes, pinguinanes, and thu-jopsanes. The sesquiterpenoids, that seem to be the most

### Table 1. Continued

| No. | *Frullania* species | Collection place | Group of compounds | References |
|-----|-------------------|-----------------|-------------------|-----------|
| 81  | *Frullania tamarisci* subsp. *tamarisci* | Cote de Jor, France; Jula, France; Vosges, France | Monoterpenes; Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes | Asakawa et al., 1979<sup>49</sup> Asakawa et al., 1980<sup>42</sup> Asakawa et al., 1991<sup>25</sup> Asakawa 1995<sup>22</sup> |
| 82  | *Frullania tamarisci* subsp. *asagrayama* | Pounds Escarpment, Illinois, USA | Oxygenated sesquiterpenes | Asakawa et al., 1979<sup>49</sup> Asakawa et al., 1980<sup>42</sup> |
| 83  | *Frullania tamarisci* subsp. *nigra* | Japan (Hirosima, Miyazaki, Hokkaido, Ehime, Kochi, Tokushima); Trasas, East Java, Indonesia | Monoterpenes; Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Bibenzyls | Asakawa et al., 1979<sup>49</sup> Asakawa et al., 1980<sup>42</sup> Asakawa et al., 1981<sup>42</sup> |
| 84  | *Frullania taradakensis* | Eugene, Oregon, USA | Sesquiterpene lactones | Asakawa 1982<sup>21</sup> Asakawa et al., 1991<sup>25</sup> |
| 85  | *Frullania tamarisci* subsp. *nigra* | Tokushima, Japan | Sesquiterpene hydrocarbons | Asakawa et al., 1980<sup>32</sup> Asakawa et al., 1981<sup>12</sup> |
| 86  | *Frullania ternatensis* | Kalimantan Seratan, Borneo | Sesquiterpene lactones | Asakawa et al., 1983<sup>44</sup> |
| 87  | *Frullania tenerifae* | Madeira: Juncal, near Fanal, Lombo dos Cedros Portugal: Estremadura | Flavonoids | Kraut et al., 1995<sup>53</sup> |
| 88  | *Frullania tolimensis* | Herbarium sample | Flavonoids | Yuzawa et al., 1987<sup>62</sup> |
| 89  | *Frullania 'truncata'* | Stewart Island, New Zealand | Sesquiterpene hydrocarbons | Asakawa et al., 2003<sup>44</sup> |
| 90  | *Frullania usamiiensis* | Ehime, Japan | Monoterpenes; Sesquiterpene hydrocarbons and lactones; Bibenzyls | Asakawa et al., 1979<sup>49</sup> Asakawa et al., 1980<sup>42</sup> Asakawa et al., 1981<sup>12</sup> |
| 91  | *Frullania wallichiana* | Herbarium sample | Flavonoids | Yuzawa et al., 1987<sup>62</sup> |
| 92  | *Frullania retusa* | Miyazaki, Japan | Sesquiterpene hydrocarbons and lactones; Flavonoids | Asakawa et al., 1979<sup>49</sup> Asakawa et al., 1980<sup>32</sup> Asakawa et al., 1981<sup>12</sup> |
| 93  | *Frullania yunnanensis* | Darjeeling, India | Monoterpenes; Sesquiterpene lactones | Asakawa et al., 1979<sup>49</sup> Asakawa et al., 1981<sup>12</sup> |
| 94  | unidentified *Frullania* sp. 1 (Venezuela) | Caracas, Venezuela | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes; Triterpenes; Bibenzyls | Hasimoto et al., 1993<sup>35</sup> Tori et al., 1995<sup>36</sup> Asakawa 1995<sup>22</sup> |
| 95  | unidentified *Frullania* sp. 2 (New Zealand) | New Zealand | Oxygenated sesquiterpenes; Triterpenes | Asakawa et al., 1996<sup>41</sup> |
| 96  | unidentified *Frullania* sp. 3 (Indonesia) | West Sumatra, Indonesia | Sesquiterpene hydrocarbons; Diterpenes; Bibenzyls; Aromatic compounds | Komala et al., 2010<sup>37</sup> |
| 97  | unidentified *Frullania* sp. 4 (Tahiti) | Mount Marau, Tahiti | Sesquiterpene hydrocarbons and lactones; Oxygenated sesquiterpenes | Komala et al., 2010<sup>37</sup> |
| 98  | unidentified *Frullania* sp. 4 | Mount Marau, Tahiti | Oxygenated sesquiterpenes | Komala et al., 2011<sup>38</sup> |

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**Chemistry of *Frullania* Species**

One of the outstanding features of the liverworts is their chemistry. They produce a wide array of secondary metabolites, and up to now over several hundred new terpenoids, and aromatic compounds including bibenzyls and bisbibenzyls with more than 40 new carbon skeletons have been isolated.<sup>16,21,22</sup> As a result of phytochemical studies, *Frullania* species are now known to produce a wide array of secondary metabolites. As shown in Table 1, 98 *Frullania* species have been chemically investigated. Most of the compounds either detected in or isolated from these species are terpenoids, aromatic compounds, and flavonoids. Among terpenoids, the sesquiterpenes are the most diverse group, but the presence of mono-, di-, and triterpenes was also confirmed. α-Pinene (1), β-pinene (2), camphene (3), δ-phellandrene (4), myrcene (5), limonene (6), and α-terpinene (7) are the monoterpenoids frequently found in *Frullania* species (Figure 1). Due to the fact that most of the *Frullania* species elaborate the same monoterpenoids, it is difficult to use them as chemosystematic markers.

In comparison to monoterpenoids, the sesquiterpenoids present in this liverwort genus are characterized by a wide range of different sesquiterpene skeletons. There are especially eudesmanes, elemenides, eremophilanes, germacranes, bazzananes, pacifigor-ganes, and other minor groups of sesquiterpenoids, like aromadendranes, africanes, barbaranes, cadinanes, cuparanes, ditaranes, farnesanes, guaianes, monocyclofarnesanes, pinguinanes, and thu-jopsanes. The sesquiterpenoids, that seem to be the most
characteristic of this genus are lactones (Figure 2). These components have been found in almost 50 Frullania species. Sesquiterpene lactones detected in and/or isolated from Frullania are mainly eudesmanolides. The most characteristic compounds belonging to this group are (+)-frullanolide (8) and (-)-frullanolide (9), but other, for example, α-(10), β-(11), and γ-cyclocostunolides (12) are also popular. Such α-methylene-γ-butyrolactones cause very strong allergic contact dermatitis. Their dihydroderivatives (13, 14) are also popular components in Frullania species but do not cause allergy.16 In the group of eudesmanolides it is also worth mentioning about rearranged spiroeudesmane-type lactones, called spirodilatanolides A-C (15-17) isolated from the European Frullania dilatata var. anomala.33

Almost all sesquiterpene lactones found in Frullania possess a 12,6-olide moiety. The exception of this rule was the isolation of densilobolides A (18) and B (19) form F. densiloba59 and eremorfrullanolate (20) together with dihydro-derivative (21) from F. lobulata, F. media, and F. proboscophora.16 The mentioned compounds have in their structures 12,8-olide moiety.

Another interesting feature of the sesquiterpene lactones occurring in Frullania is the presence of dimeric compounds. A good example is the isolation of two dimeric lactones with eudesmanolide structure called muscicolide A (22) and B (23) from the Portuguese F. muscicola.45

Frullania species, occasionally produce sesquiterpenoids which are very rare in this genus and are characteristic for just a few species. The good example is the presence of pacifigorgianes (eg, 24-26) in F. fragilifolia, as well as F. tamarisci and their subspecies. The second example are bazzarane-type sesquiterpenoids (eg, 27-29) found in F. falciloba, F. squarrosula and unidentified Frullania from New Zealand (Figure 3).16

Among the diterpenoids, labdane-, and fusicoccane-type compounds are most prevalent in Frullania, but kauranes have also been found in a few species. There are two Frullania species rich in labdane-type diterpenoids. These are F. hamatiloba and F. inouei and both produce manoyl oxide derivatives.22,40 The most characteristic components for the former species are hamatilobenes (eg., 30),22 while structurally similar labdanes, for example, 1,2-dehydro-3,7-dioxomanoyl oxide (31) were isolated from the second species (Figure 3).16

Frullania species occasionally also produce triterpenoids and these mainly belongs to oleanane, taraxane, hopane, lupane, and friedelan group. The major component of an unidentified Frullania species collected in Venezuela was methyl 3α-hydroxyolean-18-en-28-onate (32).56 F. fugax from New Zealand produces a triterpene alcohol, taraxerol, and the major component (88%),14 while α-zeorin (33) was isolated from the Argentine F. braziliensis.27 Another triterpene, friedelin, was found in F. tamarisci.21 The ether extracts from the New Zealand F. falciloba and F. squarrosula were fractionated to give epi-betulinic acid (34) (Figure 3).52

Besides terpenoids, the second group of compounds with a great diversity are bibenzyls (eg., 35-37) (Figure 4). The most abundant compounds in this group are bibenzyls possessing the methylenedioxy group. 3-Methoxy-3′,4′-methylenedioxybibenzyl (35) is the most predominant.16,21,22 In comparison to bibenzyls, their dimers called bissbibenzyls are very rare in Frullania. Such components together with acyclic bibenzyl-dihydrophenanthrenes were found in the Ecuadorian F. convoluta.30 The isolated bissbibenzyls,
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(40-43) are perrottetin-type compounds and are widespread in the Radulaceae and Marchantiaceae liverwort families. The acyclic bibenzyl-dihydrophenanthrenes, 38 and 39, seem to be good chemical markers of this liverwort, since these have been found only in this species.

Figure 2. Sesquiterpene lactones characteristic for Frullania species.

Flavonoids are ubiquitous minor components in the liverworts, also in genus Frullania. Among the flavonoids found in Frullania species more common are flavones, but also some flavanones were also detected. As in all liverworts, luteolin and apigenin derivatives dominate in this genus. It is worth
mentioning that the most common flavonoid glycosides are glucuronides, for example, luteolin-7-O-glucuronide (44), luteolin-7,4′-diglucuronide (45), or apigenin-7-O-glucuronide (48). Besides O-glycosides, flavone-C-glycosides were also found, but the most popular flavonoids are flavone methyl ethers (eg., 46, 47, 49) and hydroxy and methoxy derivatives of flavone and flavanone (Figure 5).13,16,21,22

Chemosystematic Approach

On the basis of the sesqui- and diterpenoids as well as bibenzyls composition, the Frullania species have been divided into six groups, namely, type I: sesquiterpene lactone-bibenzyl, type II: sesquiterpene lactone, type III: bibenzyl, type IV: labdane, type V: bazzanane, and type VI: pacifigorgiane-type (Table 2).

As shown in this table, the most significant markers of Frullania species are sesquiterpene lactones and bibenzyls. Five types of sesquiterpene γ-lactones have been recognized in Frullania species. There are the eudesmanolides, elemanolides, eremophilanolides, germacrnanolides, and guaianolides, and, among these, the eudesmane-type sesquiterpene lactones are the most prevalent. In case of bibenzyls found in Frullania, compounds possessing the methylenedioxy group and polymethoxylated bibenzyls occur much more often.16,21,22

Thirteen among ninety-eight chemically investigated Frullania species were classified as chemotype I. These species produce sesquiterpene lactones and bibenzyls as the main components.

South American Frullania brasiliensis belongs to the type I since it elaborates sesquiterpene lactones (eg., 8, 12, 13) and
3,3′,4-trimethoxybibenzyl.\textsuperscript{27} The most known eudesmanolide, frullanolide occurs in this species in both enantiomeric forms (8, 9). Besides eudesmanolides, this Argentine liverwort also produce eremophila-12,6-olides, 5-epi-dilatanolides A and B, which are very rare occurring lactones. Such kind of eremophilane lactones were also found in 2 more \textit{Frullania} species, \textit{F. muscicola} (type I) and \textit{F. dilatata} (type II).\textsuperscript{16}

From a Bulgarian collection of \textit{F. dilatata} var. anomala which belongs to chemotype I, unusual spiroeudesmane-type lactones (15-17) were isolated along with C12/C6- and C12/C8-eremophilanolides and common eudesmanolides, frullanolide (8) and its dihydroderivative (13).\textsuperscript{33} It is chemosystematically interesting to note that neither C12/C6 eremophilanolides nor spirolactones as well as bibenzyls have been found in \textit{F. dilatata} from French collections.\textsuperscript{16,22}

The Ecuadorian \textit{F. convoluta} is chemically very characteristic. Together with sesquiterpene lactones and bibenzyls, acyclic bisbibenzyls, perrottetins E–G (40-42), and bibenzyl-dihydrophenanthrenes (38, 39) were isolated.\textsuperscript{30} \textit{F. convoluta} is the only species that produce bisbibenzyls.

Two Venezuelan collections of an unidentified \textit{Frullania} species have been chemically analyzed. Phytochemical studies showed that one collection should be classified within type I, since it produces 3-methoxy-3′,4′-methylenedioxybibenzyl, α-cyclocostunolide (10) and rothin A acetate. The second collection showed just the presence of the mentioned sesquiterpene lactones, thus should be classified in type II.\textsuperscript{56}

\textit{F. muscicola} is another liverwort classified in chemotype I. It produces both sesquiterpene lactones and bibenzyls.\textsuperscript{22,45} This liverwort is also known for the presence of dimeric

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.jpg}
\caption{Bibenzyls and bisbibenzyls characteristic for \textit{Frullania} species.}
\end{figure}
sesquiterpene lactones, muscicolides A (22) and B (23) as well as phthalides. Two other Frullania species, *F. tamarisci* ssp. *obscura* and *F. yunnanensis*, are known for the content of eudesmanolide dimers, while phthalides has been isolated from *F. falciloba*. 41,14,16,22

Frullania vethii, which was classified in chemotype II, produces guianolides together with elemane-type sesquiterpene lactones. 21,34 Guianolides have not been detected in the other *Frullania* species so far.

The New Zealand *Frullania chevalieri* (type II) elaborates eudesmane-type sesquiterpenes. The chemical analysis of the New Zealand *Frullania chevalieri* (type II) elaborates eudesmane-type sesquiterpenoids. 22

Frullania species classified in chemotype III do not produce sesquiterpene lactones at all, but these species are known for the presence of bibenzyls. Among eleven liverworts classified in chemotype III, 8 species elaborate bibenzyls possessing the methylenedioxy group; 3-methoxy-3′,4′-methylenedioxybibenzyl (35) is the most predominant. 16,21,22

*Frullania hamatiloba* and *F. fugax* represent the labdane chemotype (IV), since both species produce structurally similar labdane-type diterpenoids. Manoyl oxide has been isolated from *F. fugax*, 14 while its derivatives, hamatilobenes A-E (eg, 30), have been found in *F. hamatiloba*. 32 A second collection of *F. hamatiloba* was found to produce structurally different labdanes. Labdane-type epoxides, has been isolated from this species together with the fusicoccane-type diterpenoids. 39 From the Chinese collection of the same species six additional labdane diterpenoids, frullanians A-F were also isolated. 40 *F. hamatiloba* is thus a really reach source of labdanoïds. Structurally similar compounds has also been found in the other Chinese *Frullania* species, *F. inouei*. From the hydroalcoholic extract of this species seven labdane diterpenoids (eg, 31) were isolated together with highly methoxylated bibenzyl derivatives. 42 The New Zealand *F. falciloba* belongs to chemotype V of the Frullaniaceae, since it elaborates characteristic bazzanane-type sesquiterpenoids (27-29), with no sesquiterpene lactones having been detected. 35 Bazzanenes A-D have been isolated from an unidentified New Zealand *Frullania* species. 11 The bazzanane sesquiterpenoids have also been found in *F. squarrosula*. 14,52

Chemical analysis of the New Zealand *Frullania falciloba* from different collections showed the presence of β-bazzanene (27), but no other bazzananes were detected. This species produces 3-methoxy-3′,4′-methylendioxybibenzyl (35), as the main component, along with the fusicoccane diterpenoid, fusicocigantepoxide. 14 On the other hand, in an Australian specimen, a large amount of the monocyclofarnesane-type sesquiterpene hydrocarbon, striatene, together with fusicoccyane-type diterpenoids has been found. 14 It is worth mentioning that the same fusicoccyanes has also been confirmed in *F. squarrosula*. 14 Further detailed analysis is required in order to investigate the chemical variations within *Frullania falciloba*.

Type VI of *Frullania* species produces the pacifigorgiane-type sesquiterpenoids. (–)-Tamariscol (24), a pacifigorgiane alcohol, has been demonstrated to be the main component in the American *F. tamarisci* and *F. tamarisci* subsp. *asagrayana*. 22,61

The same compound has also been isolated from *F. tamarisci* subsp. *tamarisci* and *F. nepalensis*, while the (+)-enantiomer has been found in the European *F. tamarisci* subsp. *obscura*. 22 Besides tamariscol (24), *F. tamarisci* produces other pacifigorgianes (eg, 26), together with the rearranged pacifigorgiane, tamariscene (25). 61 Tamariscene (25) is the major constituent of the German *F. fragilifolia*, and the other pacifigorgianes have also been found. 61

The phytochemical studies of the Asian collections of *F. tamarisci* subsp. *obscura* showed that this species is not homogeneous and should be further divided into 2 subtypes, type-T and type-O. 22 Type-T produces the usual pacifigorgiane alcohol tamariscol (24) and eudesman-4α,6α-diol as the major components, whereas type-O lacks these 2 sesquiterpenoids while eudesmanolides are predominant. 22 Representatives of type T
### Table 2. Chemotypes of *Frullania* Species.

| Type | *Frullania* species | SES | DI |
|------|---------------------|-----|----|
|      |                     | Pac | Ger | Baz | Eud | SL | Lab | Fus | BB | BB2 | AR |
| I    |                     |     |     |     |     |    |     |     |    |     |    |
|      | *F. brasiliensis*    | +   |     |     |     |+++| +   |     |     |     |    |
|      | *F. convoluta*       | +   |     |     |     |+++| +   |     |     |     |    |
|      | *F. davurica*        | +   |     |     |     |+++| +   |     |     |     |    |
|      | *F. dilatata*        |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. incumbens*       | +   |     |     |     |+++| +   |     |     |     |    |
|      | *F. momoea*          | +   |     |     |     |+++| +   |     |     |     |    |
|      | *F. muscicola*       |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. osumiensis*      |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. parvistipula*    |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. ptychantha*      |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. serrata*         |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. usamiensis*      |     |     |     |     |+++| +   |     |     |     |    |
|      | *unidentified*       |     |     |     |     |+++| +   |     |     |     |    |
|      | *Frullania* sp. 1    |     |     |     |     |+++| +   |     |     |     |    |
| II   |                     |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. apiculata*       |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. asagrayama*      |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. aterrima* var. aterrima | + |     |     |     |+++| +   |     |     |     |    |
|      | *F. aterrima* var. leptida |   |     |     |     |+++| +   |     |     |     |    |
|      | *F. biornistipula*   |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. brotheri*        |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. californica*     |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. chesalieri*      |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. congesta*        |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. densiloba*       |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. deplanata*       |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. dilatata*        |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. diversitexta*    |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. franciscana*     |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. inflata*         |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. lobulata*        |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. magellanica*     |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. mammillloa*      |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. media*           |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. nisquallensis*   |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. probosciphora*   |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. ramuligera*      |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. rostrata*        |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. scalaris*        |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. spathulopetala*  |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. tamarisci* subsp. nisquallensis |   |     |     |     |+++| +   |     |     |     |    |
|      | *F. ternatensis*     |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. vethii*          |     |     |     |     |+++| +   |     |     |     |    |
|      | *F. yunnanensis*     |     |     |     |     |+++| +   |     |     |     |    |
|      | *unidentified*       |     |     |     |     |+++| +   |     |     |     |    |

(Continued)
have been found in high mountains at 1500-3000 m altitude and in the northern part of Japan (42, 44°N), while type-O occurs more frequently at lower altitudes between 32 and 40°N.25

There are other thirty-two Frullania species difficult to classify in terms of the six chemotypes indicated above, and further chemical analysis will be necessary. However, among these species, the New Zealand F. solanderiana produces very characteristic 2-alkanones, such as 2-undecanone, 2-tridecanone, and 2-pentadecanone, as the main components.14 This is the first record of the identification of the 2-alkanones in the genus Frullania.

| Type | Frullania species | SES | DI |
|------|------------------|-----|-----|
| III  | F. amplicrania    | +   | +   |
|      | F. anomala       |     | +++ |
|      | F. boninoda      |     | +   |
|      | F. ericoides     |     | +++ |
|      | F. jackii        | +   | +++ |
|      | F. patula        | +   | +++ |
|      | F. pedicellata   |     | +   |
|      | F. pycnantha     |     | +++ |
|      | F. scandonii     |     | +++ |
|      | F. spinifera     |     | +   |
|      | unidentified     |     | +++ |
| IV   | F. fugax         |     | +   |
|      | F. hamatiloba    |     | +++ |
|      | F. inoue         |     | +++ |
|      | F. solanderiana  |     | +++ |
|      | F. squarroidea   |     | +++ |
|      | unidentified     |     | +++ |
| V    | F. falcinoba     |     | +++ |
|      | F. nepalesis     |     | +++ |
|      | F. tamarisci     |     | +++ |
|      | F. tamarisci subsp. asagrayama | + | +++ |
|      | F. tamarisci subsp. obscura | + | +++ |
|      | F. tamarisci subsp. tamarisci | + | +++ |
| VI   | F. fragilifolia  | +++ | ++ |
|      | F. neapalesis    |     | +++ |
|      | F. tamarisci     |     | +++ |
|      | F. tamarisci subsp. asagrayama | + | +++ |
|      | F. tamarisci subsp. obscura | + | +++ |
|      | F. tamarisci subsp. tamarisci | + | +++ |
|      | unidentified     |     | +++ |

Abbreviations: SES, sesquiterpenes; Pac, pacifigorgianes; Ger, germacranes; Baz, bazzananes; Eud, eudesmanes; SL, sesquiterpene lactones; DI, diterpenes; Lab, labdanes; Fus, fusioceanes; BB, bibenzyls; BB₂, bisbibenzyls; AR, aromatic compounds; MON, monoterpenes; FLA, flavonoids.
**Summary**

*Frullania* species, although morphologically simple, are characterized by enormous diversity of secondary metabolites, especially terpenoids and aromatic compounds. The most characteristic compounds present in this liverwort genus are sesquiterpene lactones with eudesmanolides as the most diverse group, and aromatic compounds belonging to bibenzyls. It was already shown that the relationship between various types of liverworts can be predicted based on the similarity or differences in the chemical substances present in them. Here, we reported the distribution of secondary metabolites in all chemically investigated *Frullania* species, and discussed some aspects concerning the division of this genus into chemotypes. Based on the chemical composition, the *Frullania* species have been divided into six chemotypes, namely, type I: sesquiterpene lactone-bibenzyl, type II: sesquiterpene lactone, type III: bibenzyl, type IV: labdane, type V: bazzanane, and type VI: pacificigorgiane-type. However, it does not appear that this research could be completed at this stage. Within some of the recognized chemotypes, there are some *Frullania* that could be divided into some sub-chemotypes, for example, *Frullania tam-arisic* subsp. *obscura*, because of the chemical differences between different collections of particular species. There are also thirty-two *Frullania* species that could not be classified into the proposed six chemotypes. Further studies on secondary metabolites occurring in liverworts are still needed. The most valuable would be those conducted in parallel with the morphological and genetic studies. Despite the fact that around one quarter of the available species have already been studied chemically and the abundance of morphological and genetic data available, it is still difficult to suggest the division of the genus into some natural sections or propose phylogenetic tree of *Frullania* genus.

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**References**

1. Schuster RM. *The Hepaticae and Anthocerotae of North America. East of the Hundredth Meridian*. Field Museum of Natural History. vol. 5; 1992:1-854.

2. Hentschel J, von Konrat MJ, Pócs T, et al. Molecular insights into the phylogeny and subgeneric classification of *Frullania Raddi* (Frullaniaceae, Porellales). *Mol Phylogenet Evol*. 2009;52(1):142-156. doi:10.1016/j.molphev.2008.12.021

3. Crandall-Stotler B, Stotler RE, Long DG. Phylogeny and classification of the Marchantiophyta. *Edinb J Bot*. 2009;66(1):155-198. doi:10.1017/s0960428609005393

4. Heinrichs J, Hentschel J, Feldberg K, Bombosch A, Schneider H. Phylogenetic biogeography and taxonomy of disjunctly distributed bryophytes. *J Syst Evol*. 2009;47(5):497-508. doi:10.1111/j.1759-6831.2009.00028.x

5. Heinrichs J, Hentschel J, Bombosch A, et al. One species or at least eight? Delimitation and distribution of *frullania tama-risi* (L.) Dumort. S. L. (Jungermanniopsida, Porellales) inferred from nuclear and chloroplast DNA markers. *Mol Phylogenet Evol*. 2010;56(3):1105-1114. doi:10.1016/j.molphev.2010.05.004

6. Odrzykoski IJ, Szewykowski J. Genetic differentiation without concordant morphological divergence in the thallose liverwort *Conocephalum conicum*. *Pl Syst Evol*. 1991;178:135-151.

7. Ludwiczuk A, Gradstein SR, Nagashima F, Asakawa Y. Chemosystematics of *Porella* (Marchantiophyta, Porellaceae). *Nat Prod Commun.*. 2011;6(3):315-321.

8. Ludwiczuk A, Odrzykoski IJ, Asakawa Y. Identification of cryptic species within liverwort *conocephalum conicum* based on the volatile components. *Phytochemistry*. 2013;95:234-241. doi:10.1016/j.phytochem.2013.06.011

9. Gradstein SR, Churchill SP, Salazar-Allen N. Guide to the bryophytes of tropical America. *Mem New York Bot Gard*. 2001;86:1-577.

10. Yuzawa Y. A monograph of subg. Chonanthelia of gen. *Frullania* (Hepaticae) of the world. *J Hattori Bot Lab*. 1991;70:181-291.

11. Hentschel J, Von Konrat M, Söderström L, et al. Notes on early land plants today. 72. Infrageneric classification and new combinations, new names, new synonyms in *Frullania* (Marchantio- phyta). *Phytotaxa*. 2015;220(2):127-142. doi:10.11646/phytotaxa.220.2.3

12. Asakawa Y, Matsuda R, Toyota M, Hattori S, Ourisson G. Terpenoids and bibenzyls of 25 liverwort *Frullania* species. *Phytochemistry*. 1981;20(9):2187-2194. doi:10.1016/0031-9422(81)80111-2

13. Krat L, Scherer B, Mues R, Sim-Sim M. Flavonoids from some *Frullania* species (Hepaticae). *Z Naturforsch C*. 1995;50(5-6):345-352. doi:10.1515/znc-1995-5-603
14. Asakawa Y, Toyota M, von Konrat M, Braggins JE. Volatile components of selected species of the liverwort genera Frullania and Schistostella (Frullaniaceae) from New Zealand, Australia and South America: a chemosystematic approach. Phytochemistry. 2003;62(3):439-452. doi:10.1016/S0031-9422(02)00542-3

15. Asakawa Y. Chemosystematics of the hepaticae. Phytochemistry. 2004;65(6):623-669. doi:10.1016/j.phytochem.2004.01.003

16. Asakawa Y, Ludwiczuk A, Nagashima F. Chemical constituents of bryophytes: Bio- and chemical diversity, biological activity, and chemosystematics. In: Kinghorn AD, Falk H, Kobayashi J, eds. Progress in the Chemistry of Organic Natural Products. Springer-Verlag; Vol 95; 2013:1-796.

17. Swain T. Chemical Plant Taxonomy. Academic Press; 1963:1-554.

18. Zidorn C. Sesquiterpene lactones and their precursors as chemosystematic markers in the tribe Cichorieae of the Asteraceae. Phytochemistry. 2008;69(12):2270-2296. doi:10.1016/j.phytochem.2008.06.013

19. Da Costa FB, Terflloth L, Gasteiger J. Sesquiterpene lactone-based classification of three Asteraceae tribes: a study based on self-organizing neural networks applied to chemosystematics. Phytochemistry. 2005;66(3):345-353. doi:10.1016/j.phytochem.2004.12.006

20. Emerenciano VP, Militão JSLT, Campos CC, et al. Flavonoids as chemotaxonomic markers for Asteraceae. Biochem Syst Ecol. 2001;29(9):947-957. doi:10.1016/S0305-1978(01)00033-3

21. Asakawa Y. Chemical constituents of the Hepaticae. In: Herz W, Grisebach H, Kirby GW, eds. Progress in the Chemistry of Organic Natural Products. Springer; 1995:1-618.

22. Yuzawa Y, Mues R, Hattori S. Morphological and chemical studies on the taxonomy of 14 Frullania species, subgenus Chonanthus. J Hattori Bot Lab. 1987;63:425-436.

23. Asakawa Y, Matsuda R, Toyota M, Takemoto T, Connolly JD, Phillips WR. Sesquiterpenoids from Claviscus, Clasmatocolea and Frullania species. Phytochemistry. 1983;22(4):961-964. doi:10.1016/0031-9422(83)8050-4

24. Asakawa Y, Matsuda R, Toyama Y, Kondo K, Hattori S, Mizutani M. Geographical distribution of tamariscol, a mossy odoriferous sesquiterpene alcohol, in the liverwort Frullania tamarisci and related species. Phytochemistry. 1991;30(7):2295-2300. doi:10.1016/0031-9422(91)83633-3

25. Mfytoyer B, Coulère P, Lebouvier N, et al. Volatile constituents of new Caledonian Frullania species. Nat Prod Commun. 2016;11(8):1934578X1601100-1934578X1601164. doi:10.1177/1934578X1601100832

26. Bdzán A, Mitre GB, Kamiya N, Toyama M, Asakawa Y. Eremophilanolidides and other constituents from the Argentine liverwort Frullania brasiliensis. Phytochemistry. 2002;59(2):205-213. doi:10.1016/S0031-9422(01)00452-6

27. Valarezo E, Tandazo O, Galán K, Rosales J, Benítez Ángel. Volatile metabolites in liverworts of ecuador. Metabolites. 2020;10(3):92 doi:10.3390/metabo10030092

28. Valarezo E, Galán K, Rosales J, Benítez Ángel. Volatile metabolites in liverworts of ecuador. Metabolites. 2020;10(3):92 doi:10.3390/metabo10030092

29. Takeda R, Ohya Y, Hirose Y. Sesquiterpenoid constituents of the liverwort Frullania brevifolia. Jpn J Pharmacol. 1983;56(4):1120-1124. doi:10.1246/bcsj.56.1120

30. Flegel M, Adam K-P, Becker H. Sesquiterpene lactones and bisbienzyln derivatives from the neotropical liverwort Frullania convoluta. Phytochemistry. 1999;52(8):1633-1638. doi:10.1016/S0031-9422(99)00200-9

31. Muess R, Hattori S, Asakawa Y, Grollie R. Biosystematic Studies on Frullania jacksonii and F. dawsonia. J Hattori Bot Lab. 1984;56:227-239.

32. Asakawa Y, Tokunaga N, Takemoto T, Hattori S, Mizutani M, Suire C. Chemosystematics of bryophytes IV: The distribution of terpenoids and aromatic compounds in Hepaticae and Anthocerotae. J Hattori Bot Lab. 1980;47:153-164.

33. Nagashima F, Takaoka S, Asakawa Y, Huneck S. New rearranged ent-eudesmane- and ent-eremophilane-type sesquiterpene lactones from the liverwort Frullania dilatata (L.) Dum. var. anomala Corb. Chem Pharm Bull. 1994;42(6):1370-1372. doi:10.1248/cpb.42.1370

34. Asakawa Y, Matsuda R, Takemoto T, et al. Chemosystematics of bryophytes VII. The distribution of terpenoids and aromatic compounds in some European and Japanese hepaticae. J Hattori Bot Lab. 1981;50:107-122.

35. Nagashima F, Toyota M, Asakawa Y. Bazzanian sesquiterpenoids from the New Zealand liverwort Frullania falciloba. Chem Pharm Bull. 2006;54(9):1347-1349. doi:10.1248/cpb.54.1347

36. Asakawa Y, Suire C, Toyama M, et al. Chemosystematics of bryophytes V: the distribution of terpenoids and aromatic compounds in European and Japanese Hepaticae. J Hattori Bot Lab. 1980;48:285-303.

37. Sass MS. Isolation and characterization of frullanolide from Frullania frutescens (Howe), Dissertations and Theses. 1981;3093

38. Toyota M, Nagashima F, Asakawa Y. Labdane type diterpenoids from the New Zealand liverwort Frullania hamackei. Phytochemistry. 1988;27(6):1789-1793. doi:10.1016/0031-9422(88)80444-8

39. Hashimoto T, Irita H, Yoshida M, et al. Chemical constituents of the Japanese liverworts Odontoschisma denudatum, Polarella japonica, P. acutifolia subsp. tisonsa, and Frullania hamatiloba. J Hattori Bot Lab. 1998;84:309-314.

40. Qiao Y-N, Sun Y, Shen T, et al. Diterpenoids from the Chinese liverwort Frullania hamatiloba and their Nrf2 inducing activities. Phytochemistry. 2019;158:77-85. doi:10.1016/j.phytochem.2018.11.002

41. Asakawa Y, Toyota M, Nakaishi E, Tada Y. Distribution of terpenoids and aromatic compounds in New Zealand liverworts. J Hattori Bot Lab. 1996;80:271-296.

42. Guo D-X, Xiang F, Wang X-N, et al. Labdane diterpenoids and highly methoxylated bibenzyls from the liverwort Frullania inouei. Phytochemistry. 2010;71(13):1573-1578. doi:10.1016/j.phytochem.2010.05.023

43. Asakawa Y, Tanikawa K, Aratani T. New substituted bibenzyls from the liverwort Frullania inouei. Phytochemistry. 2001;34(1):211-218. doi:10.1016/S0031-9422(00)09807-0
45. Kraut L, Mues R, Sim-Sim M. Sesquiterpene lactones and 3-benzylphthalides from Frullania muscicola. Phytochemistry. 1994;37(5):1337-1346. doi:10.1016/S0031-9422(00)90409-6
46. Lou H-X, Li G-Y, Wang F-Q. A cytotoxic diterpenoid and antifungal phenolic compounds from Frullania muscicola Steph. J Asian Nat Prod Res. 2002;4(2):87-94. doi:10.1080/10286020290027353
47. Tori M, Miyazaki N, Taira Z, Asakawa Y. Nepalen-solide A, novel sesquiterpene lactone from the liverwort Frullania nepalensis. Compound breaking the Samek rule. A study by NOE and X-Ray. Chem Lett. 1990;19(11):2115-2116. doi:10.1246/cl.1990.2115
48. Kim YC, da S Bolzani V, Baj N, Gunatilaka AA, Kingston DG. A DNA-damaging sesquiterpene and other constituents from Frullania nisquallensis. Planta Med. 1996;62(1):61-63. doi:10.1055/s-2006-957800
49. Asakawa Y, Tokunaga N, Toyota M, Takemoto T, Suire C. Chemosystematics of bryophytes I. The distribution of terpenoids of bryophytes. J Hattori Bot Lab. 1979;45:395-407.
50. Asakawa Y, Toyota M, Nagashima F, Hashimoto T. Chemical constituents of selected Japanese and New Zealand liverworts. Nat Prod Commun. 2008;3(2):289-300. doi:10.1177/1934578X0800300238
51. Li R-J, Zhu R-X, Zhao Y, et al. Two new cadinane-type sesquiterpenes from the Chinese liverwort Frullania serrata. Nat Prod Res. 2014;28(19):1519-1524. doi:10.1080/14786419.2014.909416
52. Asakawa Y, Toyota M, Nagashima F, Hashimoto T. Chemical constituents of selected Japanese and New Zealand liverworts. Nat Prod Commun. 2008;3(2):289-300. doi:10.1177/1934578X0800300238
53. Pannequin A, Tintaru A, Desjober J-M, Costa J, Muselli A. New advances in the volatile metabolites of Frullania tamarisci. Flavour Fragr J. 2017;1:1-10.
54. Asakawa Y, Tokunaga N, Toyota M, et al. Chemosystematics of bryophytes II. The distribution of terpenoids in Hepaticae and Anthocerotae. J Hattori Bot Lab. 1979;46:67-76.
55. Hashimoto T, Asakawa Y, Nakashima K, Tori M. Chemical constituents of 25 liverworts. J Hattori Bot Lab. 1993;74:121-138.
56. Tori M, Aoki M, Nakashima K, Asakawa Y. Terpenoids from the liverworts Symphyogyna brasiliensis and unidentified Frullania species. Phytochemistry. 1995;39(1):99-103. doi:10.1016/0031-9422(94)00846-L
57. Komala I, Ito T, Yagi Y, Nagashima F, Asakawa Y. Volatile components of selected liverworts, and cytotoxic, radical scavenging and antimicrobial activities of their crude extracts. Nat Prod Commun. 2010;5(9):1375-1380. doi:10.1177/1934578X1000500908
58. Komala I, Ito T, Nagashima F, Yagi Y, Asakawa Y. Cytotoxic bibenzyls, and germacrane- and pinguisane-type sesquiterpenoids from Indonesian, Tahitian and Japanese liverworts. Nat Prod Commun. 2011;6(3):303-309. doi:10.1177/1934578X1100600301
59. Nagashima F, Tanaka H, Takaoka S, Asakawa Y. Eudesmane-type sesquiterpene lactones from the Japanese liverwort Frullania densiloba. Phytochemistry. 1997;45(3):555-558. doi:10.1016/S0031-9422(96)00019-2
60. von Konrat M, Braggins JE, Toyota YA, Muhle H. Pacifigorgianes and tamariscene as constituents of Frullania tamarisci and Valeriana officinalis. Phytochemistry. 2001;57(2):307-313. doi:10.1016/S0031-9422(01)00018-8
61. Ludwiczuk A, Asakawa Y. Fingerprinting of secondary metabolites of liverworts: chemosystematic approach. J AOAC Int. 2014;97(5):1234-1243. doi:10.5740/jaoacint.2014.97.5
62. Ludwiczuk A, Asakawa Y. Chemotaxonomic value of essential oil components in liverwort species. A review. Flavour Fragr J. 2015;30(3):189-196. doi:10.1002/ffj.3236