NPC Natural Product Communications

2018
Vol. 13
No. 9
1205 - 1207

Phytochemistry of the Genus *Trichocolea*

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Received: April 28th, 2018; Accepted: May 30th, 2018

The genus *Trichocolea* (Fam. Trichocoleaceae) comprise 31 species of liverworts, most of which are endemic in a wide geographical area of the southern Pacific Ocean including New Zealand, Tasmania, and South Australia. Although few reports have been reported on the phytochemistry and pharmacognosy of these briophytes, data reported so far show a great pharmacological potential for their secondary metabolites. Phytochemicals isolated from *Trichocolea* spp. include benzoate esters, flavonoids, and diterpenes. The reported biological activities of these natural compounds refer to cancer cells growth inhibitory, anti-bacterial, anti-fungal, and anti-oxidant effects. The aim of this short review is to examine in detail from a phytochemical and pharmacological point of view what is reported in the current literature about the properties of phytopreparations or individual chemicals obtained from liverworts belonging to the *Trichocolea* genus.

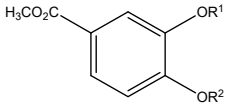
Keywords: Benzoate esters, Biological activity, Diterpenes, New Zealand, Prenyloxy secondary metabolites, *Trichocolea* spp.

1. Introduction

The genus *Trichocolea* Dumortier (order Jungermanniales, family Trichocoleaceae) comprises 31 species of liverworts having a wide geographical distribution covering the southern Pacific Ocean (South Australia, Tasmania, and New Zealand). The main botanical features of plants belonging to the title genus have been extensively reviewed by Hatcher in 1958 [1]. The pool of secondary metabolites isolated from liverworts belonging to the title genus include benzoate esters, flavonoids, and labdane and isopimarane diterpenes. Although there are no reports on the folk and ethnomedical uses of plants belonging to the *Trichocolea* genus and few citations about pharmacological activities of individual principles or phytopreparations, data currently at disposition show a great potential to this concern [2]. The aim of this short review is to examine from phytochemical and pharmacological perspectives the different species belonging to the *Trichocolea* genus for which the extraction, isolation, structural characterization, and description of the biological activity of individual compounds and/or phytopreparations are reported in the literature. A substructure search, performed in the SciFinder Scholar database, and searches by keywords in PubMed, Medline, and Scopus, indicated that to date 5 species and a total of 21 secondary metabolites have been cited in the literature. For each plant, listed in alphabetic order a discussion on its phytochemistry and pharmacognosy is provided.

2. *Trichocolea hatcheri* E.A.Hodgs

Trichocolea hatcheri E.A.Hodgs is a species endemic of New Zealand featured by a small size, dark green color, and prostrate habit. Upon microscopic analysis, tapered leaf cilia, which lack swollen septae, and weak or absent cuticular ornamentation can be observed [3]. The first phytochemical study on this species appeared in the literature in 1998 when Perry and coworkers reported the isolation and structural characterization of prenyl benzoates **1-10** [4]. These Authors preliminarily observed that an extract of this species exerted a marked cytotoxic effect on monkey kidney (BSC) cells. Subsequent bioassay-guided fractionation by reverse phase chromatography led to the isolation of compounds **1-10**.



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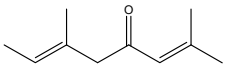
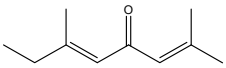
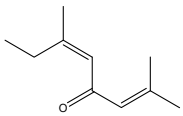
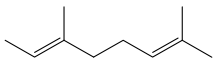
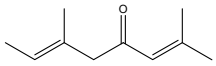
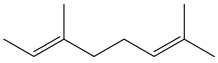
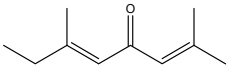
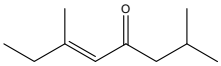
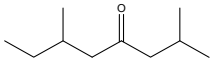
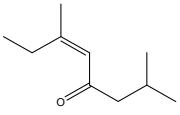
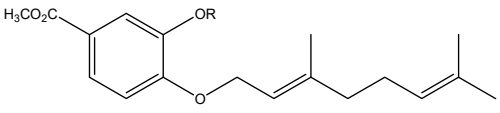
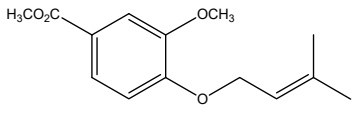
1	CH_3	
2	CH_3	
3	CH_3	
4	CH_3	
5	H	
6	H	
7	H	
8	H	
9	H	
10	H	

All the isolates are characterized by the presence of 3'-OH groups in the aromatic ring instead of the "typical" 3'-OCH_3 of the other in so far investigated *Trichocolea* spp. Thus, the presence of such a moiety can be regarded as a distinguished feature of *T. hatcheri* inside the title genus. In the same year these Authors accomplished the synthesis of compound **1**, along with two other phytochemicals, namely methyl 4-[{(2*E*)-3,7-dimethyl-2,6-octadienyl}oxy]-3-methoxybenzoate **11**, and methyl 4-[{(2*E*)-3,7-dimethyl-2,6-octadienyl}oxy]-3-hydroxybenzoate **12** by alkylation of methyl vanillate with the suitably functionalized geranyl bromide [5]. Samples **1-3** were then assayed for their cytotoxic effects in the U.S. National Cancer Institute's AIDS-related lymphoma screens. Compound **1** showed an appreciable activity in the concentration range 9.7 x 10^{-9} – 2.5 x 10^{-5} M. Compound **6** has been also screened for its cytotoxic, anti-microbial, and anti-oxidant effect, but showing only moderate activities in all tests [6]. The *in vitro* growth inhibitory effect has been evaluated in the human normal and cancer cell lines, namely NIH 3T3 fibroblasts, SK-MEL-3 (melanoma), and KB (oral cancer), recording IC_{50} values of 113.73 μM, 160.68 μM, and 11.63 respectively. The anti-microbial activity has been assessed against a panel of Gram positive and Gram-negative bacteria and fungi comprising *Streptococcus aureus* (ATCC 29213), *Streptococcus mutans* (JC-2), *Staphylococcus epidermidis* (ATCC 12228), *Pseudomonas aeruginosa* (KCTC 1636). *Pseudomonas putida* (KCTC 8729), *Candida albicans* (KCTC 1940). Compound **6** was slightly active only on *S. epidermidis* with a minimal inhibitory concentration (MIC) value of 1000 μg/mL. For what concerns the anti-oxidant activity, ascorbic acid and butylhydroxytoluene were found to be by far more active than sample 6.



11 R = CH_3, **12** R = H



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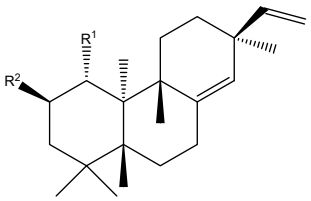


14 R^1 = OH, R^2 = H, **15** R^1 = R^2 = OH, **16** R^1 = H, R^2 = OH

3. *Trichocolea lanata* (Ehrh.) Dum.

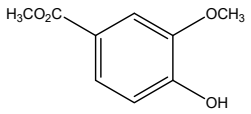
Trichocolea lanata (Ehrh.) Dum. (sin. *Leiomitra lanata* R.M. Schust.) is a species endemic of New Zealand and several isles of the southern Pacific Ocean. This liverwort is featured by a brilliant green color and the presence of overlapping leaves bearing numerous fine hairs (cilia). This liverwort lives on the forest floor and holds water with many hairs on its blades [7]. So far only one investigation has been carried out on this species and led to the isolation and structural characterization of the 3,3-dimethylallyloxy benzoate ester **13** [5]. Assayed as an *in vitro* anti-fungal agent, methyl 4-(3-methyl-2-butenoxy)-3-methoxybenzoate **13** was seen to exert only a weak activity against *C. albicans* and *Tricophyton mentagrophytes*.

4. *Trichocolea mollissima* (Hook. f. and Tayl.) Gott.

Trichocolea mollissima (Hook. f. and Tayl.) Gott., commonly known as "woollywort", is a liverwort commonly found in Australia (Tasmania, Victoria, South Wales, Queensland) and in northern New Zealand. It is featured by highly divided, densely arranged, and extremely small leaves, which lend it a woolly appearance. This liverwort typically grows in rainforest and beech forest, hanging from old tree trunks or growing erect on the forest floor [8]. The first investigation appeared in the literature in 1996 when Perry and coworkers disclosed the presence of geranyloxy benzoate derivatives **1-3** [5]. In subsequent biological assays compound **1** was seen to be highly cytotoxic *in vitro* against monkey kidney (BSC) cells at 15 μg/disk with 100% of growth inhibition and weakly active on *C. albicans* and *T. mentagrophytes*. In 1997 Lorimer and coworkers reported the isolation and structural characterization of the diterpene *ent*-1α-hydroxysandaracopimara-8(14),15-diene **14** from the ethanol extract of this liverwort. Compound **14** exhibited no appreciable pharmacological activity when assayed as an anti-microbial agent [9]. Seven years later Asakawa and coworkers recorded the presence in the same species of two additional *ent*-isopimarane-type diterpenoids **(**1R,2R)-ent-1,2-dihydroxyisopimara-8(14),15-diene **15** and (2R)-ent-2-hydroxyisopimara-8(14),15-diene **16** structurally related to **14** [10].

5. *Trichocolea pluma* (Reinw. et. al.) Mont.

Trichocolea pluma (Reinw. et. al.) Mont. is a species endemic of New Zealand, Australia, and some other islands of the Pacific Ocean. It is very similar in structure to *Trichocolea tomentella* but have the ultimate cells of cilia of leaves are much more elongated [11]. As for other *Trichocolea* species mentioned above, also for this one, prenyl 3,4-dimethoxybenzoate esters represented the most abundant phytochemicals [12]. The biosynthetic precursor of such secondary metabolites, vanillic acid methyl ester **17**, has been detected in the essential oil obtained by stem-distillation of *T. pluma* [13]. The remaining phytochemical investigations on this species reported in the literature refers to the isolation of a labdane diterpene, (-)-3α-hydroxylabda-8(17),12E,14-triene **18** [14].



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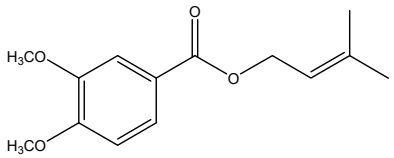

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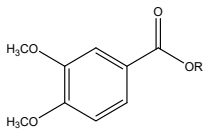
6. *Trichocolea tomentella* (Ehrhart) Dumortier

Trichocolea tomentella (Ehrhart) Dumortier, also known as "handsome woolywort" has a wide geographical distribution worldwide including north Europe, It is a large dioecious liverwort. It is conspicuous, with a characteristic greenish-white colour, highly dissected leaves and abundant paraphyllia and usually grows in moist, well-shaded places, particularly in deciduous forest, often near springs, streams or gullie [15]. *T. tomentella* is the most extensively liverwort of this genus studied from a phytochemical point of view. The first investigations on this species have been carried out between 1978 and 1981 and led to the isolation of three methoxybenzoate esters, trichocolein **18**, tomentellin **19**, and isotomentellin **20** [16-17].



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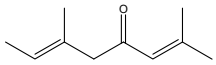

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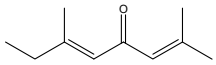

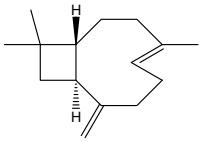

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The investigations on the essential oil composition obtained from this species allowed to identify (-)-β-caryophyllene **21** among the main components [18]. One year later compounds **1-3** and **5** have been isolated from an ethanol extract of this species. Biological assays using **5** revealed that this latter to be effectively cytotoxic *in vitro* against monkey kidney (BSC) cells at 15 µg/disk with 100% of growth inhibition, but not on P-388 leukemia cells. It was also found that this same product was slightly active against *C. albicans* and *T. mentagrophytes* [4, 19]. Finally, *T. tomentella* has been selected as an experimental model to investigate the biosynthesis of the hemi- and monoterpenyl *O*-side chains of isoprenyl ethers featuring the genus *Trichocolea* by ^{13}C incorporation studies [20].

7. Conclusions and future perspectives

In this short review we summarize the natural products isolated from liverworts belonging to the genus *Trichocolea* and analyse claims of pharmacological properties. In most cases a single compound is seen to be the effective pharmacological active agent. Nevertheless, further phytochemical studies need to be carried out in the near future to provide a more detailed pattern of the natural constituents and of the biologically active principles in extracts and/or phytopreparations from this genus. From data collected in this review, it is evident that the genus *Trichocolea* comprises therapeutically promising, interesting, and valuable species. Considering that only 5 out of 31 species of the title genus have been investigated so far and mostly only for the isolation and structural characterization of secondary metabolites, and that there are only few studies describing their pharmacological properties, this genus merits considerable attention in the on-going search for new bioactive principles and lead compounds.

References

[1] Hatcher RE. (**1958**) The Genus *Trichocolea* in New Zealand. *Transaction Proceeding of the Royal Society of New Zealand*, ***85***, 237-246.

[2] Dey A, Mukherjee A. (**2015**) Therapeutic potential of bryophytes and derived compounds against cancer. *Journal of Acute Diseases*, ***4***, 236-248.

[3] Schuster RM. (**1968**) Studies on the Hepaticae, XXIX-XLIV. A miscellany of new taxa and new range extensions. *Nova Hedwigia, **15***, 437-529.

[4] Baek SH, Perry NB, Weavers RT, Tangney RS. (**1998**) Geranyl phenyl ethers from the New Zealand liverwort *Trichocolea hatchery Journal of Natural Products*, ***61***,126-129.

[5] Perry NB, Foster LM, Lorimer SD, May BCH, Weavers RT, Toyota M, Nakaishi E, Asakawa Y (**1996**) Isoprenyl phenyl ethers from liverworts of the genus *Trichocolea*: cytotoxic activity, structural corrections, and synthesis. *Journal of Natural Products*, ***59***, 729-733.

[6] Baek SH, Oh HJ, Lim JA, Chun HJ, Lee HO, Ahn JW, Perry NB, Kim HM. (**2004**) Biological activities of methyl-4-[[(2*E*)-3,7-dimethyl-2,6-octadienyl]oxy]-3-hydroxybenzoate. *Bulletin of the Korean Chemical Society*, ***25***, 195-197.

[7] Martin W. (**1950**) The bryophytes of Stewart Island. Part II. *Transaction & Proceedings of the.Royal Society of New Zealand*, 78, 485-501.

[8] Ratkowsky DA. (**1980**) Tasmanian and New Zealand *Trichocolea* (Hepaticae). *The Bryologist*, ***1***, 78-82.

[9] Lorimer SD, Perry NB, Burgess EJ, Foster LM. (**1997**) 1-Hydroxyditerpenes from two New Zealand liverworts, *Paraschistochila pinnatifolia* and *Trichocolea mollissima. Journal of Natural Products*, ***60***, 421-424.

[10] Nagashima F, Murakami M, Takaoka S, Asakawa Y. (**2004**) *Ent*-isopimarane-type diterpenoids from the New Zealand liverwort *Trichocolea mollissima*. *Phytochemistry*, ***64***, 1319-1325.

[11] Katagiri T. (**2015**) Two new synonyms of *Trichocolea pluma*: *Trichocolea comptonii* and *Trichocolea geniculata* from New Caledonia (*Trichocoleaceae*, Marchantiophyta). *Bryophyte Diversity and Evolution, **37***, 31-34.

[12] Asakawa Y, Lin X, Kondo K, Fukuyama Y. (**1991**) Chemosystematics of bryophytes. Part 47. Terpenoids and aromatic compounds from selected east Malaysian liverworts. *Phytochemistry, **30***, 4019-4024.

[13] Ludwiczuk A, Komala I, Pham A, Bianchin JP, Raharivelomanana P, Asakawa Y. (**2009**) Volatile components from selected Tahitian liverworts. *Natural Product Communications*, ***9***, 1387-1392.

[14] Chang SJ, Wu CL. (**1987**) A new labdane alcohol from the liverwort *Trichocolea pluma*. *Huaxue,* 45, 142-149.

[15] Rydgren K, Stabbetorp OE, Blom HH (**2012**) Distribution and ecology of *Trichocolea tomentella*. *Lindbergia, **35***,1-6.

[16] Asakawa Y, Toyota M, Takemoto T. (**1978**) New aromatic esters from the liverwort *Trichocolea tomentella*. *Experientia*, ***34***, 155-166.

[17] Asakawa Y, Toyota M, Takemoto T, Mues, R. (**1981**) Chemosystematics of Bryophytes. Part 9. Aromatic esters and terpenoids of the liverworts in the genera *Trichocolea*, *Neotrichocolea*, and *Trichocoleopsis*. *Phytochemistry, **20***, 2695-2699.

[18] Fricke C, Rieck A, Hardt IH, Konig WA, Muhle H. (**1995**) Identification of (+)-β-caryophyllene in essential oils of liverworts by enantioselective gas chromatography. *Phytochemistry*, ***39***, 1119-1121.

[19] Baek SH, Perry NB, Weavers RT. (**1998**) Synthesis of geranyl phenyl ethers based on the cytotoxic monoterpenoids from the liverwort genus *Trichocolea*. *Journal of Natural Products*, ***61***, 1143-1145.

[20] Barlow AJ, Becker H, Adam KP. (**2001**) Biosynthesis of the hemi- and monoterpene moieties of isoprenyl phenyl ethers from the liverwort *Trichocolea tomentella*. *Phytochemistry*, ***57***, 7-14.