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# Prescribing Pattern of *Bryophyllum* Preparations among a Network of Anthroposophic Physicians

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## Keywords

*Bryophyllum* · *Kalanchoe* · Anthroposophic medicine · Complementary medicine · Mental and behavioral disorders

## Summary

**Background:** The use of preparations from *Bryophyllum pinnatum* for tocolysis (or to arrest labor) is supported by observations obtained mainly at empirical level, but also by preclinical experiments performed with uterus strips and myometrium cell lines. Furthermore, a retrospective matched-pair study revealed good tolerability and effectiveness. In anthroposophic medicine, however, *Bryophyllum* species are used for a broad spectrum of diagnoses. Here, we characterize the prescribing pattern of *Bryophyllum* preparations in a network of anthroposophic physicians in Germany. **Methods:** 38 primary-care physicians in Germany participated in the EvaMed network, a multi-center observational study. They documented anonymized prescriptions, diagnoses and demographic data (age and gender) for each consecutive patient between 01.01.2004 and 01.01.2010. Diagnoses were coded according to the 10th revision of the International Classification of Diseases (ICD-10). In the present analysis, all prescriptions of any *Bryophyllum* preparation in the resulting data bank were identified and the corresponding diagnoses were analyzed retrospectively. **Results:** A total of 4,038 prescriptions of *Bryophyllum* preparations were identified in the EvaMed data bank. A variety of preparations could be found, 77.7% of which were prepared from *Bryophyllum* plants exclusively and 22.5% were combinations. *Bryophyllum* preparations were often prescribed to treat 'mental and behavioral disorders' (ICD-10 F00–F99, 35.7%) and 'diseases of the skin and subcutaneous tissue' (L00–L99, 16.0%), followed by 'symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified diseases' (R00–R99, 15.2%) and 'diseases of the nervous system' (G00–G99, 9.7%). **Conclusion:** By revealing the use of *Bryophyllum* preparations in so many other indications than preterm delivery, our data clearly show the urgent need to conduct additional clinical trials.

## Schlüsselwörter

*Bryophyllum* · *Kalanchoe* · Anthroposophische Medizin · Komplementärmedizin · Psychische und Verhaltensstörungen

## Zusammenfassung

**Hintergrund:** Die Anwendung von *Bryophyllum*-Präparaten in der Behandlung von vorzeitigen Wehen wird hauptsächlich von empirischen Beobachtungen und von experimentellen Ergebnissen gestützt, die sowohl auf Organ- als auch auf Zellebene erzielt wurden. Darüber hinaus zeigte eine retrospektive Matched-pair-Studie gute Verträglichkeit und Wirksamkeit. Daneben werden in der anthroposophischen Medizin *Bryophyllum*-Arten für ein großes Spektrum von Erkrankungen eingesetzt. In dieser Arbeit wurde das Verordnungsmuster von *Bryophyllum*-Präparaten in einem Netzwerk anthroposophischer Ärzte in Deutschland charakterisiert. **Methoden:** 38 Hausärzte in Deutschland nahmen am EvaMed-Netzwerk, einer multizentrischen Anwendungsbeobachtung, teil. Zwischen dem 01.01.2004 und dem 01.01.2010 erfassten sie für jeden konsekutiven Patienten anonymisierte Verordnungen, Diagnosen und demographische Daten (Alter und Geschlecht). Die Diagnosen wurden nach ICD-10 (10. überarbeitete Auflage der International Classification of Diseases) codiert. In der vorliegenden Arbeit wurden retrospektiv aus der daraus resultierenden Datenbank alle Verordnungen von *Bryophyllum*-Präparaten identifiziert und die zugehörigen Diagnosen analysiert. **Ergebnisse:** Aus der EvaMed-Datenbank wurden 4038 Verordnungen von *Bryophyllum*-Präparaten identifiziert. Darunter fand sich eine Vielzahl an Präparaten, 77,7% davon waren reine *Bryophyllum*-Präparate und 22,5% Kombinationspräparate. *Bryophyllum*-Präparate wurden häufig für die Behandlung von «Psychischen und Verhaltensstörungen» (ICD-10 F00–F99, 35,7%) und «Krankheiten der Haut und der Unterhaut» (L00–L99, 16,0%), gefolgt von «Symptomen und abnormen klinischen und Laborbefunden, die anderenorts nicht klassifiziert sind» (R00–R99, 15,2%) und «Krankheiten des Nervensystems» (G00–G99, 9,7%) verordnet. **Schlussfolgerung:** Die Daten zeigen eine vielfältige Verordnung von *Bryophyllum*-Präparaten bei anderen Indikationen als bei vorzeitigen Wehen und legen dadurch die dringende Notwendigkeit nahe, zusätzliche klinische Studien durchzuführen.

## Introduction

*Bryophyllum* spp. have been used in ethno-medicine of the regions of origin – tropical Africa, tropical America, India, China, Australia [1] – for a long time and apparently with considerable success. In their countries of origin, leaves of these plants are used to treat jaundice [2], inflammation, infections [3], and hypertension, as well as bladder and kidney problems [4]. Furthermore, there are indications that extracts from leaves of plants of the genus *Bryophyllum* (family Crassulaceae) might have the following properties [1]: analgesic, antipyretic, sedative, central nervous system (CNS) depressant, muscle relaxant, gastroprotective, anti-inflammatory, antiseptic, anti-allergic, anti-anaphylactic, antileishmanial, antitumor, anti-ulcer, immunomodulating, and wound healing (see also [3, 5–7]). Finally, extracts of whole plants have been shown to have hypoglycemic properties, which might be useful in the treatment of diabetes [6].

In Europe, the use of remedies prepared from the species *Bryophyllum* is limited almost exclusively to anthroposophic medicine, a holistic medical system founded by Rudolf Steiner and Ita Wegman in the 1920s [8]. There are several different *Bryophyllum* preparations currently in use that are produced either from *Bryophyllum pinnatum* (Lamarck) Oken (synonym: *Kalanchoe pinnata* (Lamarck) Persoon), synonym: *Bryophyllum calycinum* (Salisbury) or from *Bryophyllum daigremontianum* (Hamet and Perrier) Berger (synonym: *Kalanchoe daigremontiana* Hamet and Perrier). To our knowledge, the only clinical trials performed so far with *Bryophyllum* preparations address their use in the treatment of women with preterm labor, i.e. for tocolysis [9]. The first studies suggesting that *B. pinnatum* could show good tolerability and effectiveness had several methodological limitations [10–12]. Later on, the effectiveness and tolerability of an aqueous extract of *B. pinnatum* leaves were compared with those of betamimetics, in a retrospective study in which data of patients with preterm contractions treated with *B. pinnatum* were matched with data of comparable patients treated with beta-agonists [13]. While the effectiveness was similar, *B. pinnatum* led to significantly fewer side effects. The use of preparations from *B. pinnatum* in the treatment of premature labor was supported by experiments performed first with a leaf aqueous extract using uterus strips [14], and thereafter conducted with press juice of leaves both at organ [15] and at cell level [16], always using experimental models that mimic uterus contractions in vitro.

Within anthroposophic medicine, the indications for which a given plant preparation is prescribed derive from hypotheses concerning the pathophysiological processes occurring in the human being and the physiological processes taking place in the plant. Depending on the part of the plant used to produce the preparation and on the pharmaceutical methods, the suggested indications can be different. In Germany, a commission was constituted to support the work of the Federal Institute for Medicinal Products and Medical Devices by providing

medical expertise in the field of anthroposophic medicine. According to this commission, *Bryophyllum* preparations are to be used for the following indications [17]: vulnerability to specific types of functional disorders and recurring infections related to the metabolic system, preterm and early contractions, and in emergency situations of anxiety or other related mental problems and associated sleep disorders. In addition, some of the multiple combinations with *Bryophyllum* preparations are indicated for mood disorders, agitation, menopausal symptoms, premenstrual syndrome, obsessive-compulsive disorders, prostration, and shock consequences [17]. There are several similarities between these indications and those suggested in another reference work on anthroposophic medicine [18], namely situations of agitation/anxiety, sleeping disorders, asthma, psychosomatic disorders, psoriasis, and neurodermitis. Anthroposophic physicians frequently rely on these 2 reference works to choose their anthroposophic medications, but it is not known whether these sources were also used by the physicians participating in the present study (see below).

The Evaluation of Anthroposophic Medicine (EvaMed) network aimed to evaluate the use of remedies from complementary and alternative medicine (CAM) in primary care with regard to prescribing patterns, efficacy, and safety [19–24]. 38 German physicians participated in this network by entering patient data on age, gender, diagnosis, and treatments. The resulting data bank has been / is being used to determine which remedies are being prescribed in general [19], which ones are prescribed for a certain diagnosis or group of diagnoses [20, 24], for a defined patient group [22, 23], and in order to characterize the prescribing pattern of a particular group of remedies [21].

Until the present work, it was not known for which exact diagnoses *Bryophyllum* preparations are being prescribed in daily clinical practice in Germany. In this country, *Bryophyllum* preparations can be obtained over-the-counter and have been in some cases officially authorized and in others registered, always without specific indications. In this work, the EvaMed data bank was used retrospectively to characterize the prescribing pattern of preparations based on *Bryophyllum* plants. It is expected that this knowledge will help in designing future clinical studies to address the effectiveness of the treatment of other disorders than preterm contractions.

## Methods

Physicians were recruited among the members of the German National Association of Anthroposophic Physicians (Gesellschaft Anthroposophischer Ärzte in Deutschland; GAÄD), which implies that all of them were specialized in anthroposophic medicine. A total of 362 physicians were contacted and informed about the EvaMed network by standard mail and, in the event of no response, 4 weeks later by telephone. For a physician to be eligible to participate in the study, he/she had to have a minimum of 5 years of professional experience and his/her medical practice had to meet a number of technical requirements, such as the presence of a special computerized patient documentation system (DocExpert,

**Table 1.** Prescribed *Bryophyllum* preparations

	Number	Percentage
<i>Bryophyllum</i> species		
<i>B. pinnatum</i>	3,830	94.8
<i>B. daigremontianum</i>	208	5.2
<i>Bryophyllum</i> monopreparations <sup>a</sup>		
<i>Bryophyllum</i> (50% powder <sup>b</sup> )*	1,063	26.3
<i>Bryophyllum Argento cultum</i> Rh (D3 aqueous dilutions)*	1,049	26.0
<i>Bryophyllum Argento cultum</i> (alcoholic dilutions <sup>c</sup> )*	693	17.2
<i>Bryophyllum</i> (alcoholic dilutions <sup>d</sup> of the mother tincture)*	135	3.3
<i>Bryophyllum Argento cultum</i> Rh (aqueous dilutions <sup>c</sup> for injections)*	47	1.2
<i>Bryophyllum</i> (5% aqueous solutions for injections <sup>c</sup> )*	43	1.1
<i>Bryophyllum Mercurio cultum</i> (alcoholic dilutions <sup>c</sup> )*	40	1.0
<i>Bryophyllum</i> Rh (D3 aqueous dilutions)*	39	1.0
<i>Bryophyllum Mercurio cultum</i> Rh (D3 aqueous dilutions)*	24	0.6
<i>Bryophyllum</i> combinations		
<i>Bryophyllum</i> D5/ <i>Conchae</i> D7 (aqueous dilutions for injections)*	687	17.3
<i>Bryophyllum</i> comp Globuli velati**	140	3.5
<i>Bryophyllum</i> comp (aqueous dilutions for injections)**	68	1.7
Dilutions		
D1–D3	2,293	54.2
50%	1,063	26.3
D5–D10	711	17.6
5%	68	1.7
Undiluted mother tincture	3	0.1

<sup>a</sup>Including preparations of *Bryophyllum* plants grown in the presence of metal dilutions (see text).  
<sup>b</sup>Dried press juice mixed with lactose.  
<sup>c</sup>D2 and D3.  
<sup>d</sup>Undiluted, 5%, D2, D3, D4, D5, D6, D8, and D10.  
\*Prepared exclusively from the species *B. pinnatum*.  
\*\*Prepared from the species *B. daigremontianum*.

DocConcept, TurboMed, Duria, AdamedPlus, Medistar), a local area network (LAN) connection, and Microsoft Windows and Internet Explorer (i.e., as client software).

A total of 38 physicians (10.5% of the physicians contacted, 6.3% of the approximately 600 physicians in GAÄD) fulfilled the various requirements, gave informed consent, and agreed to participate in this prospective, multicenter observational study. All of them became members of the EvaMed network, which aims to evaluate CAM remedies in usual care with regard to prescribing patterns, efficacy and safety [19, 22–24]. The participating physicians were from 12 of 16 German states, their average age was 48.0 ± 6.1 years and 55% of them were male; none was working in a health center. They prospectively documented anonymized prescriptions, diagnoses and demographic data (age and gender) for each consecutive patient and provided these administrative, secondary data to the EvaMed data bank. The recommendations for good practice in secondary data analysis (e.g. anonymization of data on prescriptions and diagnoses) developed by the German Working Group on the Collection and Use of Secondary Data [25] were applied in full. In addition, the study was approved by the data security office of the Community Hospital Havelhoehe, which is associated with the Havelhoehe Research Institute. As only administrative, anonymized data were used and no experimental research or intervention on patients was applied, no ethical approval was considered to be needed [26].

Prescriptions for each consecutive patient were entered in the data set by the participating physicians using their existing computerized patient documentation system. These data were thereafter exported to the Quality Documentation Statistics System in Health Care (QuaDoSta) hosted in each practice [20]. After completing each export, participating physicians

used a browser-based interface to match individual diagnoses with the corresponding drugs or remedies that had been prescribed. Finally, study investigators checked the data for completeness (e.g., matching diagnoses with remedies). If necessary, the study center phoned the physicians and asked them to supply any missing data. Diagnoses were coded according to the 10th revision of the International Classification of Diseases (ICD-10). Prescribed drugs were documented using the German National Drug Code (German: Pharmazentralnummer; PZN). The data collection covered the period from January 2004 until January 2010 (6 years).

The present retrospective analysis is based on the EvaMed data bank. Prescriptions were included in this analysis if *Bryophyllum* or one of the corresponding national codes was mentioned and if under therapy at least 1 diagnosis was mentioned. Subgroup analyses were performed for patient gender, age (younger than 12 years, 12–29 years, 30–44 years, 45–59 years, 60–79 years, 80 years or older), as well as for the various *Bryophyllum* preparations. Statistical analysis was performed with SPSS 16.0 for Windows. Descriptive analysis was used to determine prescription rates. Means and standard deviations (SDs) were calculated for continuous data.

## Results

### *Description of the Participating Physicians and Patients*

A total of 4,038 prescriptions of various *Bryophyllum* preparations were identified (table 1), corresponding to 2,280 patients; these were on average 29.5 ± 22.27 years old and in

**Table 2.** Prescribing pattern of *Bryophyllum* preparations according to ICD-10 diagnosis groups in the various gender and age groups

ICD-10 group	Designation	All (n = 4038)	Gender		Age, years					
			female (n = 2904)	male (n = 1134)	< 12 (n = 1260)	12–29 (n = 235)	30–44 (n = 865)	45–59 (n = 1130)	60–79 (n = 500)	≥ 80 (n = 48)
C00–D48	neoplasms	1.6	1.7	1.2	< 1	< 1	< 1	3.5	4.4	< 1
D50–D90	diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	< 1	< 1	< 1	1.0	< 1	< 1	< 1	< 1	< 1
E00–E99	endocrine, nutritional and metabolic diseases	1.9	2.4	< 1	< 1	< 1	1.0	2.5	5.6	< 1
F00–F99	mental and behavioral disorders	35.7	35.6	35.9	30.5	33.6	34.1	43.3	36.4	25.0
G00–G99	diseases of the nervous system	9.7	10.2	8.4	9.9	9.8	8.7	10.2	9.2	14.6
H60–H95	diseases of the ear and mastoid process	< 1	< 1	< 1	< 1	< 1	< 1	1.0	1.6	4.2
I00–I99	diseases of the circulatory system	3.9	5.0	1.2	< 1	1.3	< 1	3.9	19.8	6.3
J00–J99	diseases of the respiratory system	1.7	1.4	2.5	3.4	2.1	< 1	< 1	1.2	2.1
K00–K93	diseases of the digestive system	1.7	1.6	2.1	1.0	< 1	2.7	2.4	1.0	< 1
L00–L99	diseases of the skin and subcutaneous tissue	16.0	13.1	23.4	26.0	20.0	16.9	8.4	5.4	6.3
M00–M99	diseases of the musculoskeletal system and connective tissue	1.0	1.2	< 1	< 1	< 1	< 1	1.8	< 1	2.1
N00–N99	diseases of the genitourinary system	3.4	4.6	< 1	< 1	2.1	4.4	6.4	3.0	< 1
O00–O99	pregnancy, childbirth and the puerperium	2.6	3.5	< 1	< 1	< 1	10.6	< 1	< 1	< 1
R00–R99	symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	15.2	13.5	19.5	21.7	20.9	10.9	11.2	10.6	39.6
S00–T98	injury, poisoning and certain other consequences of external causes	1.1	1.0	1.5	1.1	1.7	1.3	1.2	< 1	< 1
Z00–Z99	factors influencing health status and contact with health services	2.2	2.7	1.0	< 1	3.4	5.2	1.9	< 1	< 1

Data are shown as % of total, only values ≥ 1% are depicted.

most cases (71.9%) female. The majority (53.2%, n = 2,150) of the prescriptions were written by general practitioners, 15.1% (n = 609) by pediatricians, 12.7% (n = 514) by internists, 10.5% (n = 424) by dermatologists, 6.5% (n = 262) by gynecologists, and 2.0% (n = 79) by neurologists. As depicted in table 2, a variety of patient age groups were well represented, even though there was a predominance of young children (31.2% of the patients were younger than 12 years) and middle-aged adults (28.0% were 45–59 years old). Relatively fewer patients were teenagers/young adults (5.8% were 12–29 years old) or older than 60 years (13.6%).

#### Prescription Characterization

As shown in table 1, most prescribed preparations had been produced with the species *B. pinnatum* (94.8%), the rest with *B. daigremontianum*. Besides the preparations depicted, a single prescription of an additional product was identified, but not included in the present analysis (data not shown). The majority (77.7%; table 1) of the prescribed preparations were produced exclusively from *Bryophyllum* plants and are in this manuscript referred to as ‘*Bryophyllum* monopreparations’, in contrast to the medications prepared with additional substances, which are referred to as ‘*Bryophyllum* combinations’. A considerable part of the former (those with names comprising the word ‘cultum’, 59.1%) were prepared from the third generation of plants whose first generation had been treated with dilutions of silver (*Argento*) or mercury (*Mercurio*) while the second and third generations were manured with the compost of the first one. This treatment is characteristic of the anthroposophic pharmacy and does not result in increased levels of the corresponding metals in the treated plants, as shown by atomic absorption (Mónica Menet, personal communication). 1 preparation included, in addition to *Bryophyllum* plants, a homeopathic dilution of oyster shell (*Conchae*). *B. daigremontianum* (D3) preparations additionally comprised a D5 dilution of silver and a D5 dilution of bovine uterus. Whereas the preparations of *B. pinnatum* were produced from fresh leaves, those of *B. daigremontianum* derive from an aqueous mother tincture of leaves that had been submitted to a fermentation process according to the technical regulation 33 from the Homeopathic Pharmacopoeia (in German: Homöopathisches Arzneimittelbuch, HAB). Finally, the preparations *Bryophyllum* (alcoholic dilutions of the mother tincture), *Bryophyllum Mercurio cultum* (alcoholic dilutions), *Bryophyllum* Rh (D3 aqueous dilutions) and *Bryophyllum Mercurio cultum* Rh (D3 aqueous dilutions) are registered in Germany; all remaining ones are officially authorised.

#### Prescribing Pattern of *Bryophyllum* Preparations

The diagnoses corresponding to the prescriptions of all *Bryophyllum* preparations taken together – for all patients according to gender and age – are depicted in table 2. Taken as a whole, *Bryophyllum* preparations were most often prescribed to treat ‘mental and behavioral disorders’ (block F00–F99,

35.7%) and ‘diseases of the skin and subcutaneous tissue’ (L00–L99, 16%), followed by ‘symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified diseases’ (R00–R99, 15.2%) and by ‘diseases of the nervous system’ (G00–G99, 9.7%). Table 2 also shows how the focus of the prescriptions varied with the age group. In the group younger than 12 years, a relatively high number of prescriptions for ‘diseases of the skin and subcutaneous tissue’ and lower use for ‘mental and behavioral diseases’ was observed. Prescriptions for symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified diseases were particularly frequent in the case of patients older than 80 years.

Table 3 shows the diagnosis categories corresponding to most prescriptions of *Bryophyllum* preparations taken as a whole and to each of the 3 most commonly prescribed monopreparations of *Bryophyllum* plants. In the first case, the following categories corresponded to more than 5% of the total prescriptions (table 3): pruritus (L29, 7.4%), sleep disorders (G47, 7.3%), depressive episodes (F32, 6.4%), other anxiety disorders (F41, 6.3%), symptoms and signs involving emotional state (R45, 5.9%), and atopic dermatitis (L20, 5.2%). Somewhat different pictures emerged for the specific preparations. *B. pinnatum* 50% powder seemed to be comparatively more often prescribed for depressive episodes and recurrent depressive disorder, other anxiety disorders, atopic dermatitis, essential hypertension, and preterm delivery. In contrast, *Bryophyllum Argento cultum* Rh (D3 aqueous dilutions) and, even more, *Bryophyllum Argento cultum* (alcoholic dilutions) were preferentially prescribed for pruritus. *Bryophyllum Argento cultum* Rh (D3 aqueous dilutions) was furthermore relatively often prescribed for (organic and non-organic) sleep disorders, symptoms and signs involving emotional state, atopic dermatitis, and (other) behavioral and emotional diseases with onset usually occurring in childhood and adolescence. Besides, for pruritus, *Bryophyllum Argento cultum* (alcoholic dilutions) seemed to be preferentially prescribed for somatoform disorders, other neurotic diseases, and other dermatitis.

#### Discussion

More than one third of the documented prescriptions of *Bryophyllum* preparations aimed at improving ‘mental and behavioral disorders’ (table 2). 3 other diagnosis groups corresponded to at least 10% of the prescriptions, namely 1) ‘skin and subcutaneous tissue’, 2) ‘symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified’, and 3) ‘diseases of the nervous system’. The frequent prescriptions for diagnoses associated with the speciality of psychiatry (F-diagnoses) even though there were no psychiatrists among the participating clinicians were not unexpected since more than the half of the participating physicians were general practitioners who often prescribe, for instance, antidepressants [27, 28].

**Table 3.** Most frequent ICD-10 diagnosis categories for which *Bryophyllum* preparations were prescribed

ICD-10	Designation	All <i>Bryophyllum</i> preparations		<i>B. pinnatum</i> (50% powder)		<i>Bryophyllum Argentocultum</i> Rh (D3 aqueous dilutions)		<i>Bryophyllum Argentocultum</i> (alcoholic dilutions)	
		n	%	n	%	n	%	n	%
L29	pruritus	298	7.4	30	2.8	101	9.6	156	22.5
G47	sleep disorders	296	7.3	60	5.6	99	9.4	37	5.3
F32	depressive episode	257	6.4	76	7.1	18	1.7	42	6.1
F41	other anxiety disorders	254	6.3	99	9.3	29	2.8	33	4.8
R45	symptoms and signs involving emotional state	239	5.9	47	4.4	90	8.6	20	2.9
L20	atopic dermatitis	211	5.2	90	8.5	76	7.2	34	4.9
F43	reaction to severe stress and adjustment disorders	181	4.5	57	5.4	17	1.6	37	5.3
F33	recurrent depressive disorder	120	3.0	62	5.8	–	–	–	–
I10	essential (primary) hypertension	117	2.9	41	3.9	–	–	–	–
F45	somatoform disorders	103	2.6	20	1.9	11	1.0	37	5.3
F51	non-organic sleep disorders	103	2.6	22	2.1	66	6.3	11	1.6
R53	malaise and fatigue	103	2.6	13	1.2	12	1.1	18	2.6
F48	other neurotic disorders	71	1.8	17	1.6	–	–	19	2.7
L30	other dermatitis	70	1.7	28	2.6	15	1.4	21	3.8
F98	other behavioral and emotional disorders with onset usually occurring in childhood and adolescence	–	–	–	–	44	4.2	–	–
O60	preterm delivery	–	–	30	2.8	–	–	–	–
R32	unspecified urinary incontinence	–	–	–	–	26	2.5	–	–
F93	behavioral and emotional disorders with onset usually occurring in childhood and adolescence	–	–	–	–	23	2.2	–	–
R63	symptoms and signs concerning food and fluid intake	–	–	–	–	21	2.0	–	–
F91	conduct disorders	–	–	–	–	18	1.7	–	–
F81	specific developmental disorders of scholastic skills	–	–	–	–	15	1.4	–	–
J06	acute upper respiratory infections of multiple and unspecified sites	–	–	–	–	13	1.2	–	–
N94	pain and other conditions associated with female genital organs and menstrual cycle	–	–	–	–	–	–	12	1.7
Z73	problems related to life management difficulty	–	–	11	1.0	–	–	–	–
R10	abdominal and pelvic pain	–	–	–	–	11	1.0	–	–
F82	specific developmental disorder of motor function	–	–	–	–	10	1.0	–	–
G40	epilepsy	–	–	–	–	10	1.0	–	–
D80	immunodeficiency with predominantly antibody defects	–	–	–	–	–	–	9	1.3
F90	hyperkinetic disorders	–	–	–	–	25	2.4	8	1.2
G43	migraine	–	–	–	–	–	–	8	1.2
N95	menopausal and other perimenopausal disorders	–	–	–	–	–	–	7	1.0

Only diagnoses corresponding to  $\geq 1\%$  of the total or of 1 *Bryophyllum* preparation are shown.

A major limitation of the present study is the lack of information on the tolerability and effectiveness of the treatment with the various *Bryophyllum* preparations. A further limitation of the study is the lack of any information on the daily dose and the duration of the application of the *Bryophyllum* preparations. Moreover, the data on the prescribing pattern have to be understood in the context of the specialties of the physicians participating in the present study: A different physician group composition would probably have led to a somewhat different weighting of the various diagnoses. Half of the participating physicians were general practitioners; therefore, this subgroup of physicians most markedly influenced the diagnosis spectrum. In the present work, the use of *Bryophyllum* preparations was not directly compared with that of other medications. Assuming, however, that the 4,038 identified *Bryophyllum* prescriptions were written at a homogeneous rate during the study period, the number of prescriptions per year would be approximately 673, which at least in 2005 [19] would correspond to about 0.9% of all prescriptions of anthroposophic medications. This estimated percentage is markedly inferior to the 9.4% that have been previously reported in a prospective cohort study on chronic diseases involving 131 medical practices in Germany [8]. It is worth noting that the physicians were free to prescribe multiple and different types of medications for 1 diagnosis. At least in 2005, anthroposophic medications corresponded to 41.8% of all medications prescribed by the physicians participating in this network of anthroposophic physicians, while conventional medications corresponded to 41.4% of the total [19].

Several components have been identified in leaves from *B. pinnatum* preparations, which are likely to have biological activity, namely flavonoid glycosides [29, 30], flavonoids [30–32], bufadienolides [33, 34], and phenols [35]. Previous work on the pharmaceutical characterization of an aqueous extract directly obtained from juice of *B. pinnatum* leaves and identical to the starting material to produce each of the three most commonly prescribed monopreparations of *Bryophyllum* plants (*B. pinnatum* 50% powder, *Bryophyllum Argento cultum* Rh D3 aqueous dilutions and *Bryophyllum Argento cultum* alcoholic dilutions) revealed the presence of flavonoids, cinnamic acid derivatives, and bufadienolides [15]. Even though these three preparations have *B. pinnatum* leaves as common plant material, their preparation methods as well as the available concentrations are different. The 50% powder is produced by mixing press juice of *B. pinnatum* with the same weight of lactose hydrate. In contrast, both preparations of *Bryophyllum Argento cultum* are homeopathic preparations. *Bryophyllum Argento cultum* alcoholic dilutions are produced from an alcoholic mother tincture that is homeopathically diluted (potentized) to the concentrations D2 (1%) and D3 (0.1%). *Bryophyllum Argento cultum* Rh is prepared from an aqueous mother tincture produced in a particular process in which the extraction temperature is changed rhythmically; thereafter, it is potentized at D3 (0.01%). The different ex-

traction methods are likely to result in different biochemical compositions. Whether these and the different concentrations can provide a rationale for their different therapeutic use requires further investigations.

Although it is difficult at present to propose a rationale for most of the detected uses of *Bryophyllum* preparations, in some cases there is preclinical evidence suggesting therapeutic potential of extracts from leaves of these plants. Their use in the treatment of pruritus – whose standard treatment is based on antihistamines (H1 antagonists) – is one of these examples. Press juice of *B. pinnatum* leaves was shown to possess antihistamine activity by blocking H1, but not H2, receptors, an effect that has been allocated to a flavonoid fraction [36]. Furthermore, an extract from *B. pinnatum* leaves has been shown to down-regulate pro-anaphylactic inducing immune responses [37] and very recently to have potential in the treatment of allergic airway disease [38].

Sleep disorders constitute a second example in which preclinical evidence might support the therapeutic use of extracts of *Bryophyllum*. Different fractions of the leaf extract of *B. pinnatum* have been shown to potentiate the pentobarbitone-induced sleeping time in in vivo models, i.e. to possess a CNS-depressant action [39]. This neurosedative effect was corroborated by a later study that in addition revealed muscle-relaxant properties of a leaf extract of *B. pinnatum* [40]. Muscle-relaxing effects of aqueous extracts from *B. pinnatum* leaves are particularly well-documented in the case of preterm uterus contractions both at the clinical level [13] and in vitro, using strips of myometrium [14, 15].

Other promising properties of *Bryophyllum* preparations comprise anti-inflammatory and wound-healing effects of *B. pinnatum* leaves [5], which were detected in an in vivo model and could justify their use in the treatment of various kinds of dermatitis, in particular that of atopic dermatitis, a chronic inflammatory skin condition. Moreover, hypotensive properties of *B. pinnatum* leaves have been demonstrated in an in vivo model [41].

## Conclusion

*Bryophyllum* preparations were prescribed by physicians participating in the EvaMed network for a broad spectrum of diagnoses, which is typical for anthroposophic preparations. The most frequent diagnosis groups were: 1) ‘mental and behavioral disorders’, 2) ‘disorders of skin and subcutaneous tissue’, 3) ‘symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified’, and 4) ‘diseases of the nervous system’. Future research should focus on pragmatic clinical trials to investigate the effectiveness of *Bryophyllum* preparations in the treatment of the most relevant clinical disorders mentioned in this report, in particular of sleep and anxiety disorders, as well as of depressions and atopic dermatitis.



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