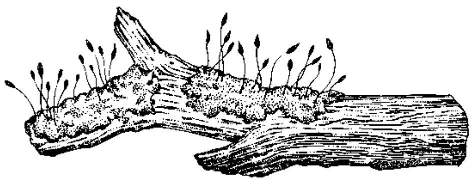

Wilton Ricardo Sala de Carvalho

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Tese apresentada ao Instituto de Biociências da Universidade de São Paulo, para a obtenção de título de Doutor em Ciências Biológicas, na área de Botânica.

Orientadora: Prof[a]. Dr[a]. Cláudia Maria Furlan

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Universidade de São Paulo. Instituto de Biociências. Departamento de Botânica.

Comissão Julgadora:

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Prof(a). Dr(a).

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Prof(a). Dr(a). Cláudia Maria Furlan
Orientadora

“Tudo o que você realmente precisa saber
no momento é que o universo é muito mais
complicado do que se poderia pensar”

(Douglas Adams, Guia do Mochileiro das Galáxias)

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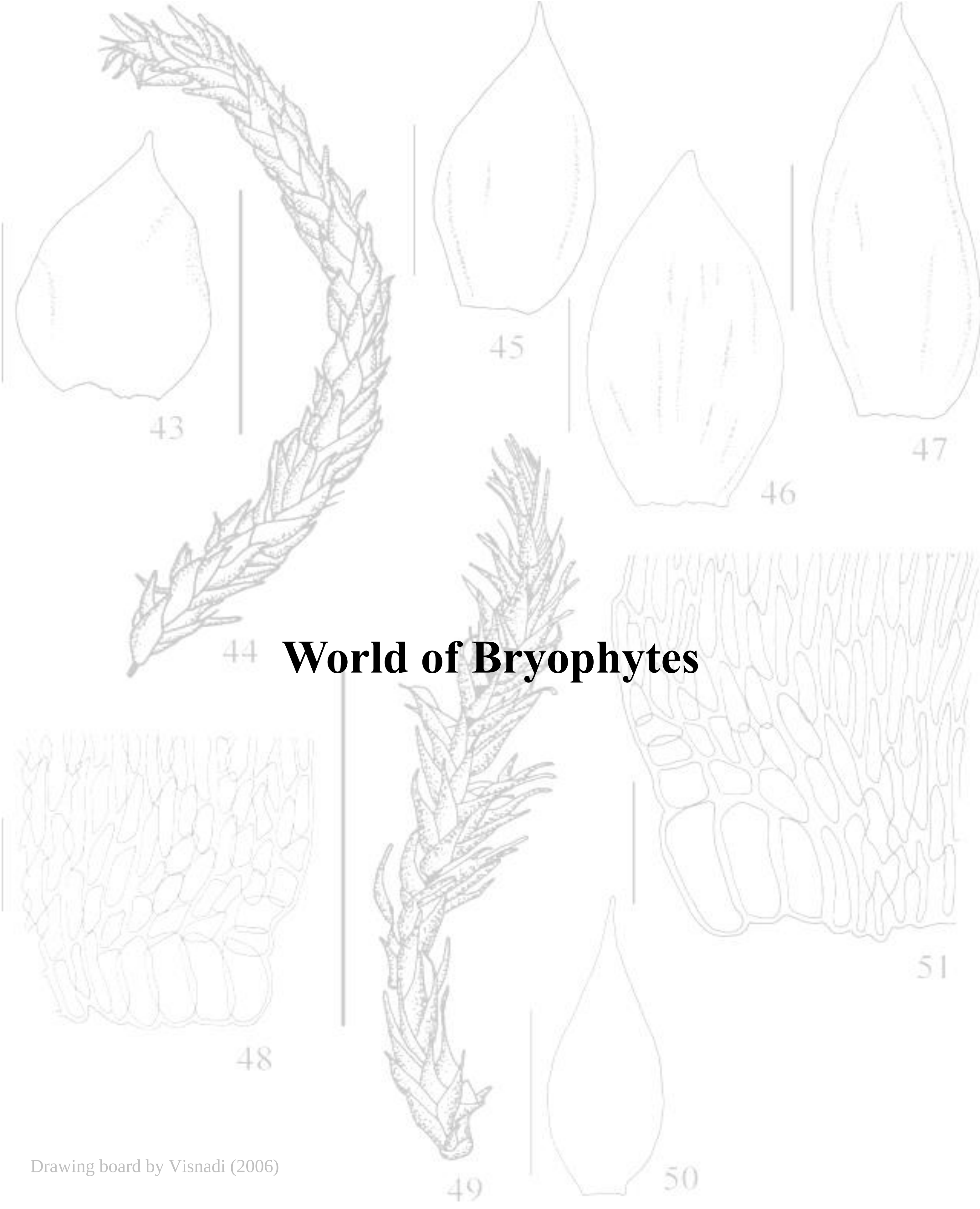
Espero não ter esquecido ninguém, aos que esqueci me perdoem, mas são muitos nomes para lembrar e poucas páginas para escrever!

Summary

World of Bryophytes



Drawing board by Visnadi (2006)

1. Taxonomy, anatomy and distribution

Spore fossils registers indicate that land colonization by plants began during Ordovician period, around 461 to 472 Ma, with the emergence of a common ancestor of embryophytes (Kenrick et al., 2012).

The bryophyte group is represented by three lineages that were previously considered paraphyletic: Marchantyophyta (Liverworts), Anthocerotophyta (Hornworts), and Bryophyta (Mosses). This is the second largest group of land plants and essential for the understanding of plant evolution. Previous evidence indicate liverworts as the first diverging lineage from embryophytes, sister to all groups of land plants (Von Konrat et al., 2010a).

These concepts (no-monophyly of bryophytes and liverworts as the first diverging lineage of embryophytes) are being questioned and going through changes after transcriptomic studies. Such studies verified the formation of a monophyletic clade composed by liverworts and mosses (Setaphyta), with the uncertainty of the hornworts position, related to tracheophytes and green algae. Recent analyses support the monophyly of bryophytes (Puttick et al., 2018).

These group of plants evolved key adaptations mechanisms to cope with both biotic and abiotic stresses, and contain many unique chemical compounds with high biological and ecological relevance (Commisso et al., 2021).

Worldly estimative suggest about 20,000 bryophytes species (Schofield, 2000), being around 11,000 mosses (Magill, 2010), 7,500 liverworts (Von Konrat et al., 2010b), and 300 hornworts (Villarreal et al., 2010). However, there is an increasing number of new species being discovered annually, mainly due to not thoroughly explored areas, and this number tends to increase (Schofield, 2000; Von Konrat et al., 2010b).

Regionally, the Brazilian bryoflora comprises 117 families, 413 genera, and 1,524 species. Among this high number of species, 880 correspond to mosses, 633 liverworts, and 11 species are hornworts (Costa and Peralta, 2015).

Regarding the Brazilian phytogeographycal domains, Atlantic rainforest is the one with the highest number of bryophytes (1,337 species, 242 endemic) being the diversity and endemic moss center. It is due to climate conditions, such as humid climate with rains distributed alongside the year, mist in mountain regions and wide range of average temperature according to land elevation, which favors a great number of microhabitat and complex topography (Costa and Peralta, 2015). Amazon rainforest (570 species and 52 endemics) and Cerrado (478 species and 63 endemics) are the other two Brazilian biomes with high number of species (Costa and Peralta, 2015).

World of Bryophytes

The bryophytes possess a noticeably ecological importance in their occurrence environment, constituting a great part of biodiversity from pluvious forests, swamps, mountains, and tundra. In temperate forests the group contributes to community structure and ecosystem work; in artic regions it is important in the permafrost maintenance and as carbon reservoir (Hallingbäck and Hodgetts, 2000).

In general, bryophytes contributes to water retention, as an important component to biogeochemical cycles, recently exposed environments colonizers, soil stabilizers, humus accumulators, turf formers and in relationships with animals species (Hallingbäck and Hodgetts, 2000).

The bryophytes are being used as bioindicators to evaluate air pollution in many regions, being used in their evaluation not only their chemical characteristics, but also their biodiversity in the studied local (Hallingbäck and Hodgetts, 2000; Oishi and Hiura, 2017), being used as bioindicators of environmental conditions indicators (Hallingbäck and Hodgetts, 2000).

Furthermore, Bryophytes, mainly mosses, are present in India's traditional medicine for burn and external lesions treatments (Alam, 2012). Azuelo et al. (2011), verified that 31 bryophytes species are medicinally used in Philippines, of those 19 are mosses and 12 liverworts, used in many treatments, such as, burns, lesions, fever, diuretics, inflammation, bleeding and other kinds of illness.

In a review by Chandra et al. (2017), it was reported the use of 50 bryophytes species in traditional medicine throughout the world, in countries such as, Poland, Argentina, Australia, Turkey, Japan, Taiwan, Pakistan, Nepal, China, India, and New Zealand. Bryophytes are generally used for the treatment of liver diseases, ocular, cardiovascular, nervous system, inflammation and surgery curatives (*Sphagnum* spp.); of those 50 species, 17 are from liverworts, 32 from mosses, and one hornwort.

Works that verified the biological activity of some species, as the study by Klavina et al. (2015) reinforce the mosses medicinal importance, in which 13 mosses extracts showed antimicrobial activity against Gram-positive and Gram-negative bacteria. There are reports of many compounds isolated from bryophytes with high antitumor activity, as reported by Asakawa and Ludwiczuk (2017).

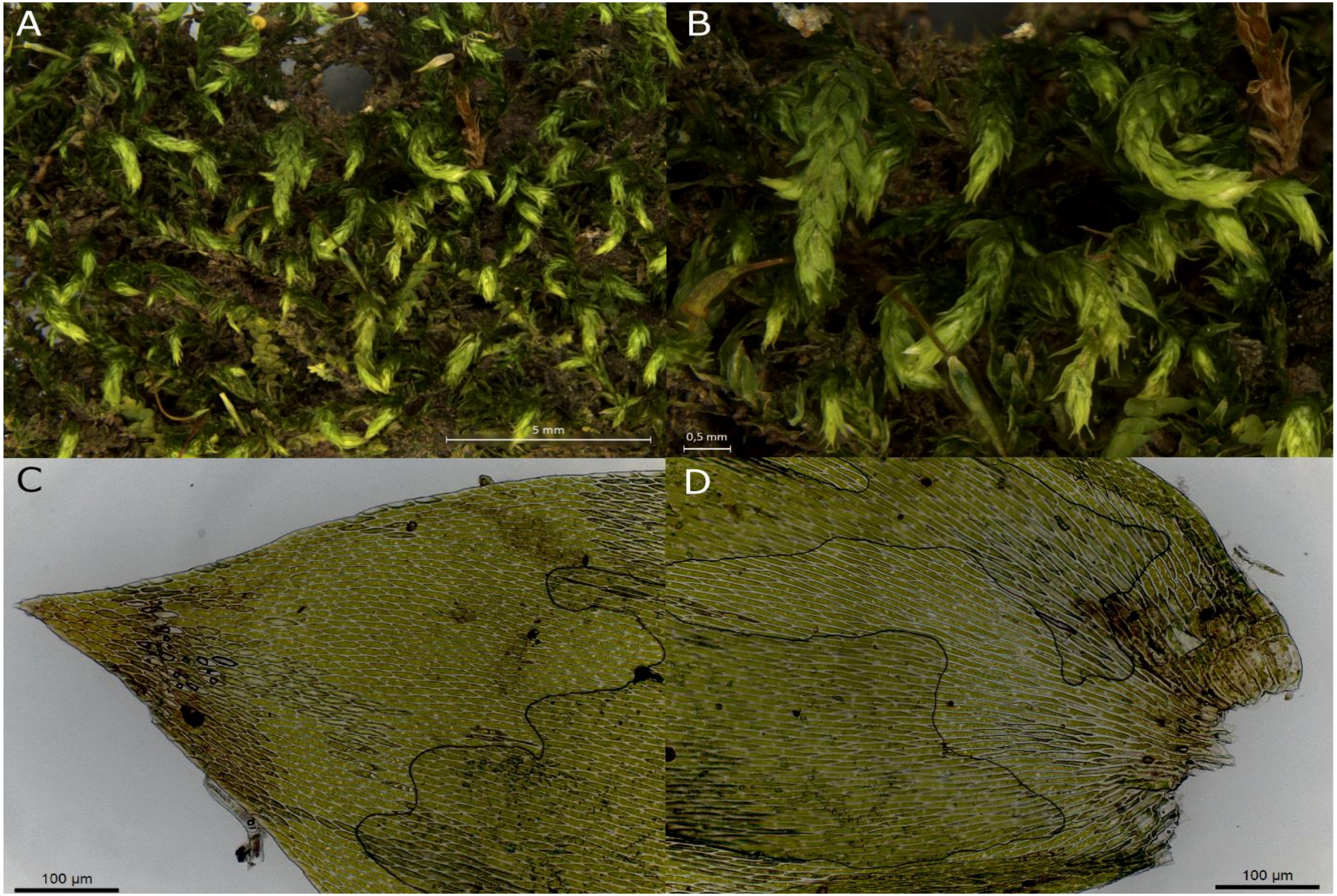


Figure 1. Pictures representing the main *Brittonodoxa subpinnata*. **A**: Gametophyte with curved apex and dark green color, which becomes clearer as it reaches the apex; **B:** Gametophyte with zoom; **C**: Photo from the short enlarged superior cells; **D**: Photo of the enlarged, little inflated color alar cells.

Final Considerations

Mosses are divided into 226 families with 1,315 validated genera (Magill, 2010). In Brazil, the ten families with most diversity are: Sphagnaceae (83 species), Fissidentaceae (65 species), Pottiaceae (63 species), Dicranaceae (54 species), Bryaceae (53 species), Semathophyllaceae (53 species), Orthotrichaceae (51 species), Pilothricaceae (51 species), Calymperaceae (48 species) and Hypnaceae (28 species), with Sematopyllaceae as the second family with most endemic species (17 endemic species) (Costa and Peralta, 2015).

Sematophyllaceae (Hypnales) is a widely distributed family throughout the globe, with diversity centers in Southeast Asia and neotropical forests, being the family circumscription still unstable (Carvalho-Silva et al., 2017). The family is one of the most diversified families of pleurocarpous mosses comprising 46 genera (Han and Jia, 2021). Of the 53 Brazilian species of Sematophyllaceae, 47 occurs in Atlantic rainforest (13 endemic) and 19 in Cerrado areas (da Costa and Luizi-Ponzo, 2010).

In a research conducted by Carvalho-Silva et al. (2017), using eight molecular markers from nuclear, mitochondrial and chloroplast genome, was verified that most genera within Sematophyllaceae are non-monophyletic, but the relationship between various species are weakly supported and the data does not permit to reject the hypothesis of monophyly of these genera.

In another work conducted by Han and Jia (2021) using five molecular markers from nuclear, mitochondrial, and chloroplast genome revealed the monophyly of Semathophyllaceae s.l. (Sematophyllaceae s.str. + Pylaisiadelphaceae), and proposed its division into six subfamilies, Taxithelioideae, Isopterygoideae, Pylaisiadelphoideae, Aptychelloideae, Platygyrioideae, and Sematophylloideae.

Brittonodoxa subpinnata (Brid.) W.R. Buck, P.E.A.S. Câmara & Carv.-Silva is a medium size pleurocarpic moss having golden-green plants; branched stems; ovate to oblong-ovate leaves, long, acute or short-acuminate, absent costa, shorter and mostly rhomboid cells in the acumen; enlarged, little inflated color alar cells, with colors varying through red to yellow brownish; 5 to 10 mm setaewith suberect capsules. The main characteristics of this species gametophyte are the curved apex and the dark green color, which becomes clearer as it reaches the apex, it is hard with short-enlarged superior cells (Figure 1) (Ramsay, 2012; Sharp et al., 1994). The species has wide distribution in Brazil, occurring in terrestrial, rupicolous, corticolous, and epixylic substrates, in Cerrado, Atlantic rainforest and Amazon rainforest domains (Carvalho-Silva et al., 2017; Peralta and Yano, 2008; Visnadi, 2004).

2. Hypothesis and Objectives

It is of common knowledge that specialized metabolites function as a chemical interface between the organism and the surrounded environment, being their synthesis influenced by different biotic and abiotic factors, being this kind of relationship well studied in angiosperms (Gobbo-Neto and Lopes, 2007; Kutchan, 2001).

Despite believing that environmental factors also affect the metabolic profile of bryophytes, only recently studies are being conducted. It is estimated that only 5% of bryophytes was chemically studied (Alam, 2012; Asakawa and Ludwiczuk, 2017), most by Japanese researchers (Alam, 2012), revealing a lack of knowledge regarding Brazilian species. The most chemically characterized species belong to the liverworts, while only 3.2% of mosses, and 8.8% of hornworts (Provenzano et al., 2019).

Despite the few interests, reports about changes in metabolic profile, in response to environmental conditions in mosses exist. In a research by Bragazza and Freeman (2007), was verified an inverse relationship between available nitrogen and polyphenol concentration, demonstrating the environmental influence over the chemical profile of bryophytes.

Clarke and Robinson (2008), observed that mosses species from Antarctic have higher phenolic compound concentration associated to cell wall, which can confer tolerance to this extreme environment, due to protection against UV radiation.

All these relationships demonstrate the necessity to deepen the metabolomic research of mosses species with occurrence in different biomes.

Based on the above, this study has as premises:

1 – As in angiosperms, the metabolism of bryophytes is influenced by environmental conditions, despite this group of land plants showing fewer phenolic compound diversity compared to angiosperms.

2 – The same species occurring in different biomes must have different metabolic profile, quantitatively.

3 – The same species occurring in the same biome must have different seasonality metabolic profile, varying according if it is rainy or dry season.

For the low amount of phytochemical research with *Brittonodoxa*, the present work proposes to analyze the metabolome of two population of *Brittonodoxa subpinnata* occurring in Atlantic rainforest and Cerrado over two periods of saplings: rainy and dry seasons. The aims of this study are to contribute to the chemical diversity knowledge of Brazilian bryoflora and to better understand the relationship between moss metabolism and the environment conditions.

Therefore, this thesis is divided in three chapters:

Chapter 1 – A Chemistry review of the beautiful miniature forest know as mosses.

Chapter 2 - Metabolome of *Brittonodoxa subpinnata*, a Brazilian native species of moss.

Chapter 3 – Ecometabolome of *Brittonodoxa subpinnata*.

Final Considerations

3. Areas used for plant collection

All samples, in all the areas, were collected under the authorization of Sistema Nacional de Gestão do Patrimônio Genético e do Conhecimento Tradicional Associado (SISGEN), under the number AA37B2E. Also, all collections had permissions granted by local authorities when in closed park areas.

Clustered samples of *Brittonodoxa subpinnata* (Brid.) W.R. Buck, P.E.A.S. Câmara & Carv.-Silva were collected in two typical areas of Cerrado located in the rural zone of Brotas (22º14’03”S 47º50’56”W – 720 m.a.s.l. – 2018 and 2019) and in Mogi-Guaçu (22º15’03”S 47º09’26”W – 630 m.a.s.l. –2018 and 2019), and in two areas of Atlantic Rain Forest reserves located in CUASO (Cidade Universitária “Armando Salles Oliveira”; 23º33’58”S 46º43’49”W – 770 m.a.s.l. – 2018 and 2019) and in Paranapiacaba (23º46’46”S 46º18’25”W – 800 m and 23º46’48”S 46º17’56”W – 800 m.a.s.l. – 2019 and 2020).

The samples from each location were deposited in “Maria Eneyda P. Kaufmann Fidalgo” Herbarium from Environmental Research Institute (IPA) under the register numbers SP505624 (Brotas), SP505623 (Mogi-Guaçu), SP505622 (CUASO).

Brotas is located at the central region of São Paulo state, in an approximate area of 11,000 ha, with two aquifers units: Guarani aquifer (sedimental) and Serra Geral aquifer (fractured), with the main river from the region being the Jacaré-Pepira river (Trevisan et al., 2017). The county is located at the Morphostructural Unity of the Paraná Sedimentary Basin and of Paulista Western Plateau, presenting geology of sandstone, pluvial sandstone, volcanic stones, and recent deposits from the Quaternary (Trevisan et al., 2017).

The region belongs to phytogeographic domain of cerrado, with its climate being classified as altitude tropical with dry winter, the annual pluviosity is of 1,350 mm, with an average temperature of 21.8 ºC. This type of climate has rainfalls throughout all months of the year, with greater amount during the summer and reducing during the winter, with high influence from tropical oceanic atmospheric system, explaining this great pluviosity and thermal variation (Guerrero et al., 2020; Trevisan et al., 2017).

The main forest formation is the Seasonal Semideciduous Forest, with cerrado vegetation formation elements, but the natural vegetation is suppressed due to the intensive historical agricultural activity of this region (Guerrero et al., 2020; Trevisan et al., 2017).

The samples were collected in the farms located at the rural region of Brotas, therefore with human influence, but in fragments with high incidence of trees, with forestall physiognomy.

Campininha farm is located at the city of Mogi-Guaçu with and average altitude of 600 m.a.s.l., in an area of approximate 470 ha, being composed by one biological reserve, and two stations, one experimental and one ecological, with a Red-Yellow Latosol type of soil (Neto et al., 2012).

The climate is classified as hot and humid, with dry winter, with an annual pluviosity of 1,481 mm, and with a minimum temperature of 18ºC and a maximum temperature of 32ºC (Neto et al., 2012).

The main forest formation is Cerrado, varying from cerradão to campo, some areas of *Pinus* cultivation, riparian forests in the south part as a riverside formation without the influence of Mogi-Guaçu river (Neto et al., 2012).

The samples were collected at the ecological station of Institute of Environmental Research (IPA), with a preserved cerradão physiognomy.

The CUASO reserve is located at University of São Paulo, with an altitude varying from 725 to 775 m.a.s.l., in an approximate area of 10.21 ha, located at São Paulo basin (Silva, 2007). The reserve is formed tertiary and quaternary deposits, with soil essentially composed by clay, acidic, poor in nutrients, and with high levels of aluminum (Silva, 2007).

The climate is classified as rainy temperate, characterized by a hot and humid summer and a cold and dry winter, with an annual average pluviosity of 1,207 mm, oscillating from an average pluviosity of 230 mm in January to 40 mm in August, the average temperature is 19.2 ºC, oscillating with an average between 14ºC (June) and 23 ºC (February) (Silva, 2007).

The Reserve main part is covered by secondary wood, forming a mosaic composed by a myriad of degradation and regeneration stages, representing one of the few remnants of forestry cover in São Paulo city. The reserve is considered a region under a climate with transitional characteristics, resulting in an ecotonal forest, with elements of Atlantic rainforest and semi-deciduous seasonal forests from the interior of São Paulo (Silva, 2007).

Despite being localized in the middle of São Paulo city, the samples were collected at the edge of the biological reserve of CUASO, a reserve with a forestall physiognomy, but with a major influence of human action in its surroundings.

PNMNP (Parque Natural Municipal Nascentes de Paranapiacaba) is located in Santo André city with altitude varying from 780 to 1174 m.a.s.l., in an approximate area of 400 ha where the source of river Grande, the main river responsible for forming the Billings dam, is found (Lima et al., 2011). The park has a crystalline geological base located in the Paulistano plateau, the frequent and abundant rains makes the landslides frequents (Lima et al., 2011).

The climate is classified as tropical with warm summer and absence of a dry season, the annual pluviosity is of 1,850 mm, with an average temperature of 22.5 ºC, and a minimum temperature of 14.7 ºC. The relative air humidity is of 93%, with winds blowing in the S and SW direction during the morning and N and NW direction during the hotter period of the day, transporting the pollutants form the industrial zone directly to the park (Lima et al., 2011).

The region is covered by Montana Dense Rainforest, secondary in the largest part of its extension, but relatively conserved in some parts. The part located at the limits of the park does not have characteristics from mature forest, mainly because of the extensive wood explotation from the past (Lima et al., 2011).

The samples were collected at the biological reserve of PNMNP, a preserved area with forestall physiognomy, with low direct influence of human action, but its location is influenced by the air pollutants produced by the surrounding industries.

The total of clustered samples collected was 64, being eight for each season (dry and rainy) and area (Brotas, Mogi-Guaçu, CUASO, and Paranapiacaba).

The plant material has been cleanup to remove most of the dirty and other species of bryophytes occurring together, and to separate the gametophyte for chemical analyses, since in the dry season the occurrence of samples with sporophyte are scarce.

Final Considerations

Despite the importance of mosses in many countries as in traditional medicine, in biomonitoring and bioremediation programs, and for their ability to survive in adverse environments, they have been poorly studied. This scenario has been changed in the last two decades, with an increase of 43% in the number of papers published in the last 17 years focusing on moss chemistry. Despite this change of scenario, only 3% of the moss species were chemically investigated, indicating a sub-valorization of mosses.

This scenario tends to change as new analytical equipment, which uses small amounts of samples and faster analysis protocols, decreasing cost of analysis, and emergence of new bioinformatic and dereplication tools are being made available for the researchers use.

The present work was devised to contribute to the chemical knowledge of mosses, using modern bioinformatic and dereplication tools, such as MzMine and GNPS. For this purpose, 4 types of extract were analyzed.

The polar extract was majorly composed by soluble sugars, amino acids and glycerol esters; the non-polar extract was majorly composed by lipids, such as fatty acids, alkane, alkene, and also by steroids; the soluble extract showed high content of glycosylated flavonoids and isoflavonoids, and the insoluble extract presented biflavonoids. The presence of biflavonoids was expected since it is a class of compounds with many reports in Hypnales, and also present in the more derived clades of mosses.

Both the location and season of plant collection are factors influencing the moss metabolome, especially considering the amplitude of fluctuation of the season's conditions in the same location.

The environmental conditions which most influenced *B. subpinnata* composition were temperature, air humidity, and solar radiation. This species presented metabolite fluctuation according to the environmental conditions, regardless the phytogeographycal domain.

We were able to annotate 189 peaks, but the total number of peaks in the four extracts were of 928, still leaving a gap for future discoveries. The use of more expensive techniques, such as isolation of compounds for NMR identification, and/or the use of non-open source chemical databases containing more MS^2 spectra compounds in the library could be an alternative to increase the number of annotated peaks.

This study was able to report about 20% of *B.subpinnata* metabolome, contributing with the chemical knowledge of one species from Hypnales and providing a small contribution to the chemotaxonomy of bryophytes, a theme approached in the first chapter, and a considerably important contribution to the knowledge of the seasonal chemical changes in this species in its natural environment.

Abstract

Bryophyte is the second major land plant group. Traditionally the group is divided into three lineages, Marchantyophyta (Liverworts), Anthocerotophyta (Hornworts), and Bryophyta (mosses), all of them with great ecological importance. Worldly, it is estimated to be around 19,000 species, being 11,000 of mosses, 7,500 of liverworts, and 200 hornworts. In Brazil are reported 117 families and 413 genera, with the occurrence of 1,524 species (880 moss species, 633 of liverworts, and 11 of hornworts). Despite its great biodiversity, there are few chemical studies using bryophytes. Fewer are the studies involving the relationship between the environmental conditions and the species metabolic profile, the chemical interface between the plant and their site of occurrence. Metabolomic is a tool that consist in quantify and characterize dataset about the metabolites of a biological matrix using different techniques (GC, HPLC) coupled to different detectors (DAD-UV/Vis, NMR, MS), together with dereplication techniques to increase the work efficiency. Due to the great ecological importance of this group of plants and the few chemical studies reported in the literature, this study aimed to contribute to the knowledge of the chemical diversity of the Brazilian bryoflora. A literature search was performed in major scientific databases, such as SciFinder, Web of Science, PubMed, Scielo, and Reaxys, using the combination of keywords bryophytes and compounds, chemical constituents, substances, phenolic, chemical characterization, and extract. Only a small percentage of moss species were chemically studied with a significant number of studies being published in the last decade. The emergence of new equipment, which can produce high-resolution spectra with small amounts of sample, combined with bioinformatic tools, can contribute to the increase of chemical investigation of mosses. *Brittonodoxa subpinnata*, a species that can be naturally found in Brazil, was chosen for this study, collected in 4 areas (2 in Cerrado and 2 in Atlantic rainforest domain) and in two seasons (dry and rainy). The plant material was frozen, crushed and submitted to two extractions: 1. methanol followed by partition with chloroform and water, for GC-MS analysis; 2. methanol 80% followed by alkaline hydrolysis to obtain the soluble and insoluble fractions (cell wall conjugated) for HPLC-MS^2 analysis. The dataset was analyzed and dereplicated using mainly GNPS library and Reaxys, SciFinder, and NUBBEdb as databases. The results were correlated with the environmental conditions of each site of plant occurrence. A total of 928 peaks were detected in the four extracts analyzed, of those only 189 (20.4%) peaks were annotated, with the major classes being sugars, fatty acids, flavonoids and biflavonoids. Three of the four environmental conditions analyzed had a significant influence over the abundance of the compounds in the samples: high temperature and air humidity being the most correlated to higher abundances, followed by solar radiation.

Resumo

Briófita é o segundo maior grupo de plantas terrestres. Tradicionalmente é dividido em três linhagens, Marchantyophyta (Hepáticas), Anthocerotophyta (Antóceros), and Bryophyta (Musgos), todos com uma grande importância ecológica. Mundialmente estima-se cerca de 19000 espécies, sendo 11000 de musgos, 7500 de hepáticas e 200 de antóceros. No Brasil, são reportados 117 fámilias e 413 gêneros, com ocorrência de 1524 espécies (880 de musgos, 633 de hepáticas, e 11 de antóceros). Apesar de sua grande biodiversidade, existem poucos estudos químicos com Bryophyta. Menores são os estudos envolvendo a relação entre condições ambientais e o perfil metabólico, a interface química entre a planta e seu local de ocorrência. Metabolômica é uma ferramenta que consiste em quantificar e caracterizar um conjunto de dados sobre os metabólitos de uma matriz biológica usando diferentes técnicas (CG, HPLC), acoplado a diferentes detectores (DAD-UV/Vis, RMN, MS), juntamente com técnicas de desreplicação para aumentar a eficiência de trabalho. Devido à grande importância ecológica desse grupo de plantas e aos poucos estudos químicos reportados na literatura, este estudo teve por objetivo contribuir com o conhecimento sobre a diversidade química da brioflora Brasileira. Foi feita uma busca nas maiores bases de dados científicas, como SciFinder, Web of Science, PubMed, Scielo, e Reaxys, usando uma combinação da palavra-chave bryophytes com compounds, chemical constituents, substances, phenolic, chemical characterization, e extract. Somente uma pequena porcentagem das espécies de musgos foram quimicamente estudadas, com a maioria dos estudos sendo publicados na última década. O surgimento de novos equipamentos, que podem produzir espectros de alta resolução com pequenas quantidades de amostras, combinado com ferramentas de bioinformática, podem contribuir para o aumento da investigação química em musgos. *Brittonodoxa subpinnata*, uma espécie achada naturalmente no Brasil, foi escolhida para este estudo, coletada em 4 áreas (2 no cerrado e 2 no domínio da Mata Atlântica) em duas estações (seca e chuvosa). O material vegetal foi congelado, pulverizado e submetido a dois processos de extração: 1. Metanol seguido por uma partição com clorofórmio e água, para análise por CG-MS; 2. Metanol 80% seguido por hidrólise alcalina para obter uma fração solúvel e uma insolúvel (conjugado da parede celular) para análise por HPLC-MS^2. O conjunto de dados foi analizado e desreplicado usando principalmente a biblioteca do GNPS e as bases de dados Reaxys, SciFinder, e NUBBEdb. Os resultados foram correlacionados com as condições ambientais de cada local de coleta.. Um total de 928 picos foram detectados nos quatro extratos de *B. subpinnata* analisados, desses somente 189 (20,4%) dos picos foram anotados, com a maioria sendo açucares, ácidos graxos, flavonoides e biflavonoides. Três das quatro condições ambientais analisadas tiveram influência significativa sobre a abundância dos compostos nas amostras: temperatura e umidade do ar sendo as mais correlacionadas com maiores abundâncias, seguido pela radiação solar.

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