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Research Article

Genetic Diversity and Its Relationship of *Dendrobium* (Orchidaceae) Based on Bioactive Compounds and Their Biological Activities: A Meta-Analysis

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Abstract: Information on genetic diversity and its relationship is fundamental for the preservation and improvement of orchid germplasm. For *Dendrobium*, such information, particularly by a meta-analysis, was limited. The study aimed to assess the genetic diversity and relationships of *Dendrobium* germplasm based on bioactive compounds, their biological activities, and plant organs by a meta-analysis approach. A total of 51 species of *Dendrobium* have been collected and identified as producing bioactive compounds, including their biological activities and plant organs (parts). In this case, the highest genetic diversity was shown by polyphenols (H' index = 0.90) as substances, neuroprotective (H' = 0.80) for activity, and the leaf organ with an H' index of 0.89. The UPGMA analysis showed that *Dendrobium* grouped into seven clusters, where the furthest relationship was presented by *D. moschatum* and *D. catenatum*. However, the closest relation was by *D. scabrilingue* with *D. delacourii*, including *D. snowflake* and *D. ovatum*. Following these parameters, *Dendrobium* shows unique genetic diversity and relationships. Thus, it is valuable for future preservation and improvement programs of *Dendrobium*.

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1. Introduction

Orchid is the second largest flowering plant (Angiospermae), with more than 28 000 species recorded worldwide (Zhang et al., 2022). This genetic resource is essential for edible, ornamental plants, and as a raw material for medicinal and pharmaceutical purposes (Wang et al., 2018). For example, *Dendrobium*, with more than 1 500 species present and spread across the tropics and subtropics (Zheng et al., 2018; Wang, 2021), is one of the orchid genera with the second-highest export value worldwide, with transactions reaching US$ 5.6 million (De et al., 2014). Furthermore, *Dendrobium* has been used for a thousand years by traditional Asian communities, especially in China and India, as a tonic or herbal to treat various diseases, such as inflammation, pyretic, and cancer (Cakova et al., 2017; Zhao et al., 2019). Consequently, on the one hand, many bioactive compounds have been explored massively from these *Dendrobium* species. On the other hand, breeding efforts to assemble new *Dendrobium* cultivars are also being carried out.

For years, three colorful flowers of *Dendrobium*, i.e., yellow, yellow-white, and purple-white, including sweet smell characteristics, have been modified to make novel hybrids or cultivars (Sawettalake et al., 2017; Li et al., 2021). In this case, over 8 000 *Dendrobium* hybrids or cultivars have been developed by inter-specific hybridization related to flower morphological characteristics (Pongsrila et al., 2014). However, this success is not directly proportional to its existence in the wild. Most wild *Dendrobium* species are susceptible and decrease due to deforestation, natural fragmentation of habitats, and other factors (Hinsley et al., 2018). Further, some are listed as endangered status in the CITES (Convention on International Trade in Endangered Species) Appendix II, e.g., *Dendrobium aberrans* (from Papua New Guinea), *D. acutimentum* (Indonesia), *D. acutilingue* (Philippines), and *D. alabense* (Malaysia) (CITES, 2023). The International Union for Conservation of Nature and Natural Resources also reported some endangered *Dendrobium*, for example, *D. whistleri*, *D. flexicaule*, and *D. leptocladum* (IUCN, 2023).

Thus, the assessment and evaluation of these genetic resources are urgent. Conventionally, comparative morphology and anatomy are familiar in determining or assessing the diversity and relationships of *Dendrobium* (Adams, 2011). However, these two approaches have certain limitations due to the high variability of these orchids. Sometimes, the results are confusing due to environmental factors. Hence, further study needs to be employed by more strong characteristics than morphological and anatomical ones. One of which is biochemical marker application. While this marker is less effective than molecular, the data are beneficial for ensuring quality, efficacy, and safety in the herbal medicine sector (Gahlawat et al., 2017). Besides, analysis of diversity and genetic relationships of *Dendrobium* using biochemical markers is rarely reported or carried out.

In this case, analysis of diversity and genetic relationships of germplasm can be employed by meta-analysis approach. According to Deshmukh (2021), meta-analysis is a statistical combination of results from two or more separate studies extracted from aggregate data of published articles. Then, in addition to being effortless, simple, and low-cost, it can overcome the constraints of formal statistical techniques by aggregating the results of individual experiments to draw general conclusions (van de Wouw et al., 2010). Following Simske (2019), this approach shows high efficiency and is comprehensible to the entire gamut of data science. Several studies using this technique, such as van de Wouw et al. (2010), in evaluating genetic diversity trends in crop cultivars from the twentieth century, and Saputra et al. (2021) for swamp and river buffalo haplotype diversity based on the *cytochrome b* gene. For *Dendrobium*, such studies have never been reported. Thus, this study aimed to assess the genetic diversity and its relationship of *Dendrobium* germplasm based on bioactive compounds, their biological activities, and the type of plant organs by a meta-analysis approach. As a hope, the results of this study provide novelty and good benefits to support future *Dendrobium* breeding and conservation programs.

2. Material and Methods

2.1. Data collection

This study was conducted using a meta-analysis approach, initially by collecting, tabulating, and analyzing various data based on literature searching. A total of 51 species of *Dendrobium* have been collected and identified as producing bioactive compounds, including their biological activities (Table S1, see supplementary file).

2.2. Data analysis

The data obtained were then analyzed in a multivariate manner using a numerical taxonomy approach by the MVSP ver. 3.1 (Kovach, 2007). The genetic diversity of *Dendrobium* was determined using the Shannon-Weaver index (H') by criteria: maximum, H = 1.00; high, H = 0.76–0.99; moderate, H = 0.46–0.75; and low, H = 0.01–0.45 (Mursyidin and Khairullah, 2020). Reconstruction of genetic relationship using cluster analysis with UPGMA (unweighted pair group of arithmetic means) method and MVSP ver. 3.1 (Kovach, 2007). The relationship was evaluated by principal component analysis (PCA) (Das et al., 2017).

3. Results and Discussion

Bioactive compounds are necessary as raw drug materials for pharmaceutical and medicinal purposes (Atanasov et al., 2021). Most of such materials are obtained from nature today (Atanasov et al., 2021). According to Srivastava et al. (2014), the primary source of drugs comes from medicinal plants and has been explored for the foundation of systematic conventional medicinal products worldwide. In this study, *Dendrobium* was identified as containing dominant compounds, i.e., flavonoid and bibenzyl (Figure 1), as reported similarly by Wang (2021).

According to Hostetler et al. (2017), flavonoids are secondary metabolites belonging to the phenolic class (because they have polyphenolic groups) and are present in various plants, including food sources such as fruits and vegetables. In general, these metabolites are involved in the interaction of plants with their environmental conditions, and hence they are particularly substantial for ecological functions, e.g., allelopathy, animal attractants, seed distribution, and biochemical defense against bacteria, bugs, and herbivores (Srivastava et al., 2014).

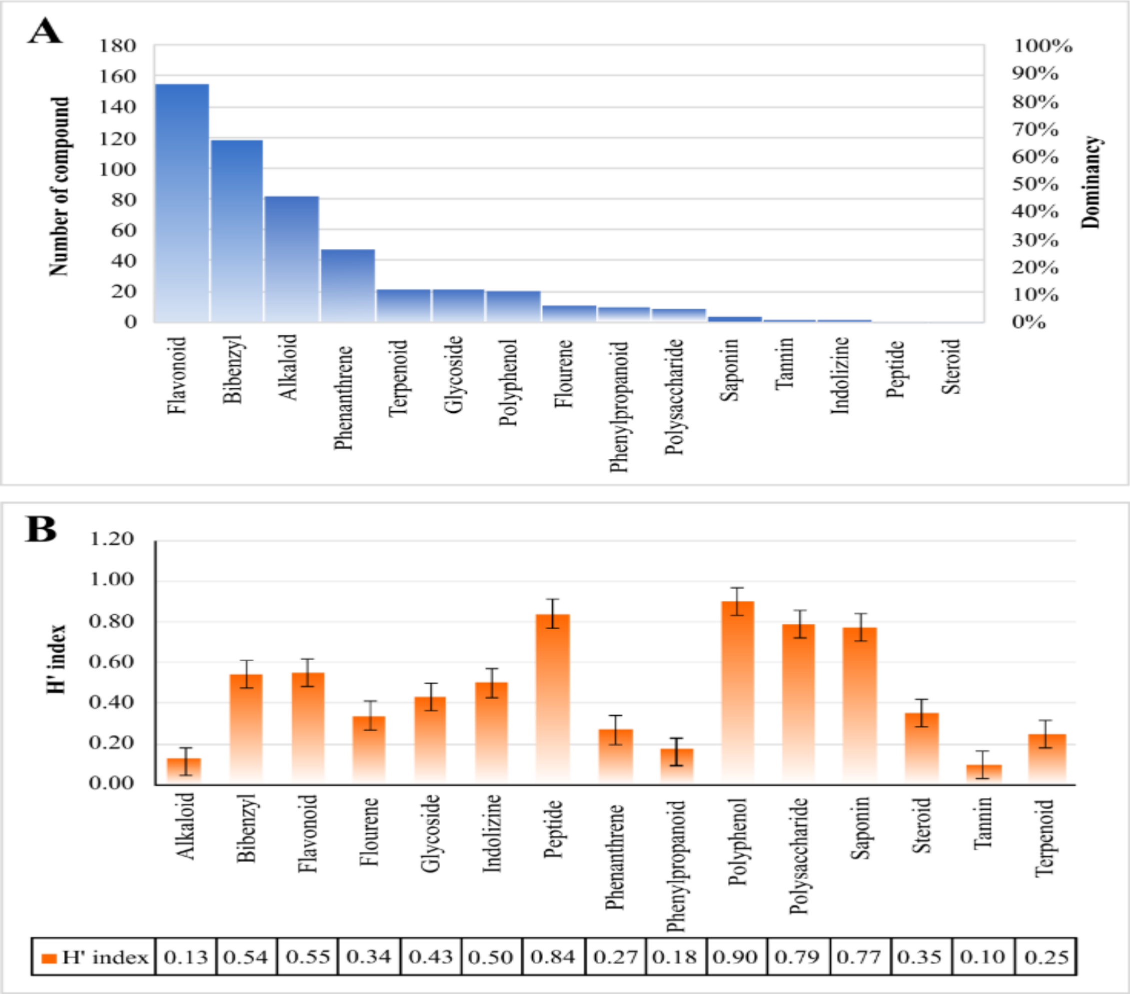

Figure 1. Bioactive compounds found in *Dendrobium*: dominancy (A) and its genetic diversity (B).

In particular, flavonoids have essential biological roles in diverse organisms (Kumar and Pandey, 2013). In plants, for example, this compound is synthesized by the phenylpropanoid pathway and has urgent responsibilities in pigmentation and fragrance in flowers, including attracting pollinators in seed or spore germination and fruit dispersion (Kumar and Pandey, 2013). Furthermore, flavonoids protect plants from many abiotic and biotic stressors, including frost hardiness, drought tolerance

(Panche et al., 2016), and microbial infection (Kumar and Pandey, 2013). Recently, these compounds have been responsible for many pharmacological activities (Kumar and Pandey, 2013).

Meanwhile, bibenzyls are a secondary metabolite distinguished structurally by the absence and presence of two phenyls connected with ethane (C_6-C_2-C_6). Bibenzyls are fragrant chemicals found in plants and bryophytes (Nandy and Dey, 2020). It is generated from the phenylpropanoid biosynthesis pathway and belongs to the polyketide family. This pathway comprises numerous secondary metabolites (Chen et al., 2022). Furthermore, bibenzyls are the synthetic precursors of dihydrophenanthrenes. He et al. (2017) reported twenty-three bibenzyls with flexible structures. For *Dendrobium*, 89 bibenzyl derivatives were present (He et al., 2020).

Interestingly, bibenzyl and flavonoids are interrelated in the biosynthetic pathway (Ahmad et al., 2022). In this case, the difference lies in the enzyme binding to substrates. For example, as a member of the polyketide synthase, chalcone synthase catalyzes the Claisen cyclization to create chalcones and dihydrochalcones (bibenzyl derivates), which are required for flavonoid biosynthesis (Chen et al., 2022). According to Lei et al. (2018), 31 unigenes annotated by the Kyoto Encyclopedia of Genes and Genomes (KEGG) database were engaged in flavonoid pathways by bio-modification, accumulation, transportation, and controlling process.

However, recent interest in the substances of bioactive compounds has shown the potential health benefits. In this study, the bioactive compounds of *Dendrobium* show the highest antioxidant, anticancer, and anti-inflammatory activities (Figure 2). According to Kumar and Pandey (2013), flavonoids' functional hydroxyl groups, for example, can mediate antioxidant effects by neutralizing metal ions and scavenging free radicals. Furthermore, these chemicals are linked to a broad spectrum of health-promoting effects and are essential for nutraceutical, pharmacological, medical, and cosmetic applications (Panche et al., 2016). Beneficial biochemical and antioxidant effects have even been linked to many diseases, such as Alzheimer's, atherosclerosis, cancer, and others (Panche et al., 2016).

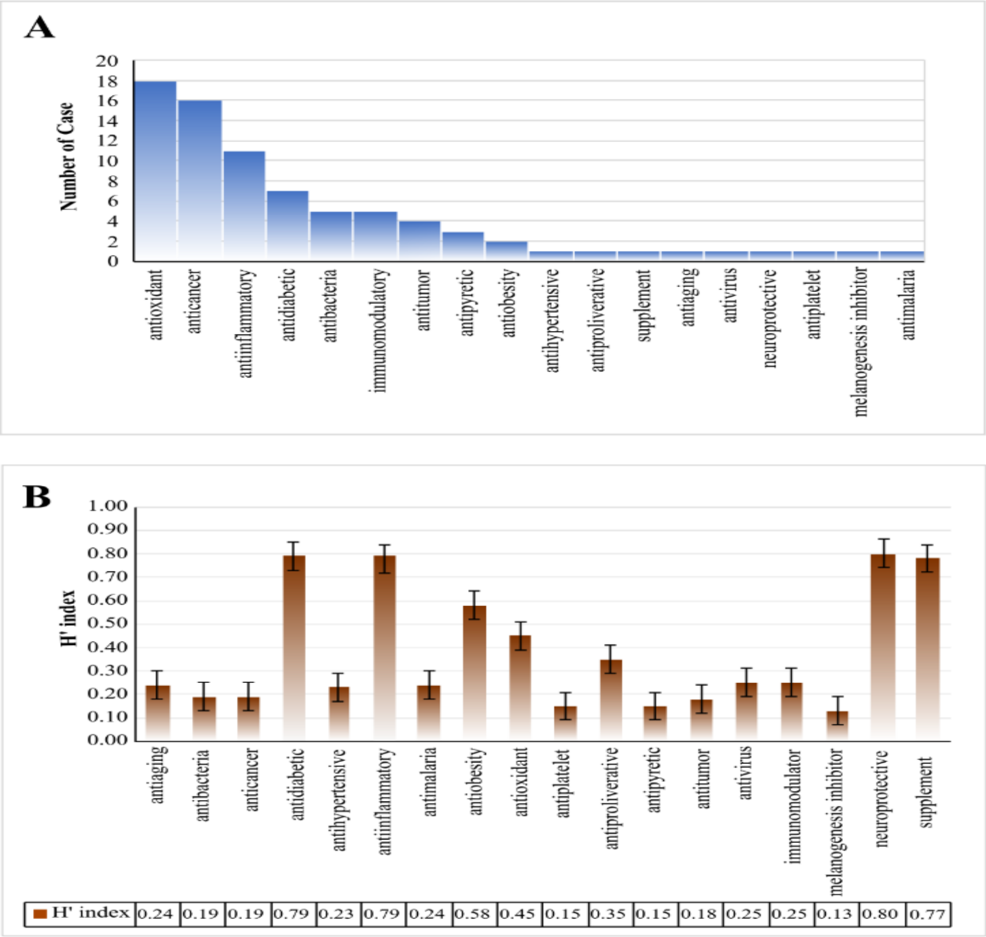

Figure 2. The activity of bioactive compounds found in *Dendrobium*: dominancy (A) and its genetic diversity (B).

Regarding the plant parts used, although the leaf has the highest H index of diversity, i.e., 0.89, the stem is the most widely used with dominance of 90%, followed by the whole part of the plant (Figure 3). In traditional medicine, several parts or plant organs are common, such as roots, stems (barks), leaves, flowers, fruits, or seeds (Srivastava et al., 2014; Khan and Ahmad, 2019). However, as the need for bioactive substances has grown, so has the exploitation of medicinal plants. As a result, alternative technologies for producing metabolites from plants on a big scale without damaging their natural population are urgent (Cragg and Newman, 2013).

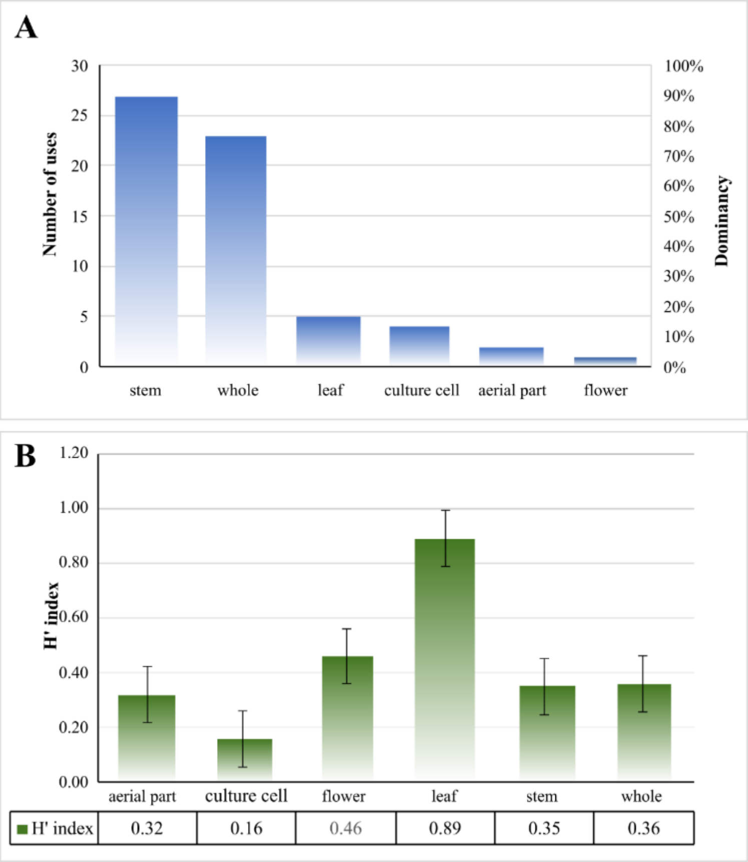

Figure 3. Plant organ and related source of *Dendrobium* which is widely used as a producer of bioactive compounds: dominancy (A) and its genetic diversity (B).

Initially, researchers tried to domesticate or cultivate medicinal plants to support conservation efforts (Phondani et al., 2016). However, due to rapid changes or replacement market demand, the cultivator finds it difficult to choose and decide which plant species to plant (Chen et al., 2016). In addition, most of the medicinal plants come from natural seeds (wild populations) (Hilonga et al., 2019). Generally, these seedlings have low germination rates or specific ecological requirements, making them hard to plant. For example, *Cymbidium* and *Phalaenopsis* are famous orchids that bloom after 2-3 years of vegetative phase (Ahmad et al., 2022).

Another issue is the lack of knowledge about pollination, seed germination, and growth in medicinal plant production (Febjislami et al., 2019). Domestic production of medicinal plants is a potential conservation method that lowers misidentification, genetic and phenotypic diversity, extract variability and instability, hazardous components, and contamination in herbal extracts (Guo et al., 2009; Chen et al., 2016). In this case, biotechnology allows for plant cells, tissues, organs, or entire organisms by cultivating them in vitro to obtain desired substances (Panche et al., 2016; Alamgir, 2018).

Many biotechnological procedures, such as elicitation, embryogenesis, cell line screening, media modification, and organogenesis, have recently been formulated to enhance the secondary metabolites production from medicinal plants (Mohaddab et al., 2022). Cell cultures containing bioactive compounds are collected at a specified period (typically during the stationary phase of their development cycle), dried, extracted, identified, and quantified (Twaij and Hasan, 2022). The core notion of plant cell suspension is biosynthetic totipotency, in which each cell in the culture preserves the complete genetic information for the range of chemical creation (Fazili et al., 2022).

Then, apart from the essential value of the bioactive and the activities, information on the genetic diversity of *Dendrobium* is also urgent and needed. According to Govindaraj et al. (2015), genetic diversity is necessary to develop a new line population for future evolutionary processes and adaptive environmental changes. Hence, this parameter is critical for future preservation and improvement programs for endangered plants (Lloyd et al., 2016; Mursyidin, 2022). For preservation, assessing genetic diversity has a beneficial impact on increasing the effectiveness and efficiency of that program (Salgotra and Chauhan, 2023).

Similarly, this parameter becomes more valuable in the context of climate change for plant breeding efforts (Govindaraj et al., 2015). In this case, high levels of genetic diversity are beneficial in promoting population survival and adaptive potential guarantee in the face of rapidly changing environmental factors (Teixeira and Huber, 2021). In other words, preserving genetic diversity is urgent in retaining their capability for the current and future crop breeding programs (Swarup et al., 2021).

Besides genetic diversity, analysis of genetic relationships is also a valuable parameter for plant conservation and breeding programs. In this study, the UPGMA analysis showed that *Dendrobium* grouped into seven clusters (Figure 4), where the furthest relationship was presented by *D. moschatum* and *D. catenatum*. Meanwhile, the closest relation was by *D. scabrilingue* with *D. delacourii*, including *D. snowflake* and *D. ovatum* (Figure 5). The PCA shows a different grouping from the UPGMA, where *Dendrobium* was separated into six clusters (Figure 6).

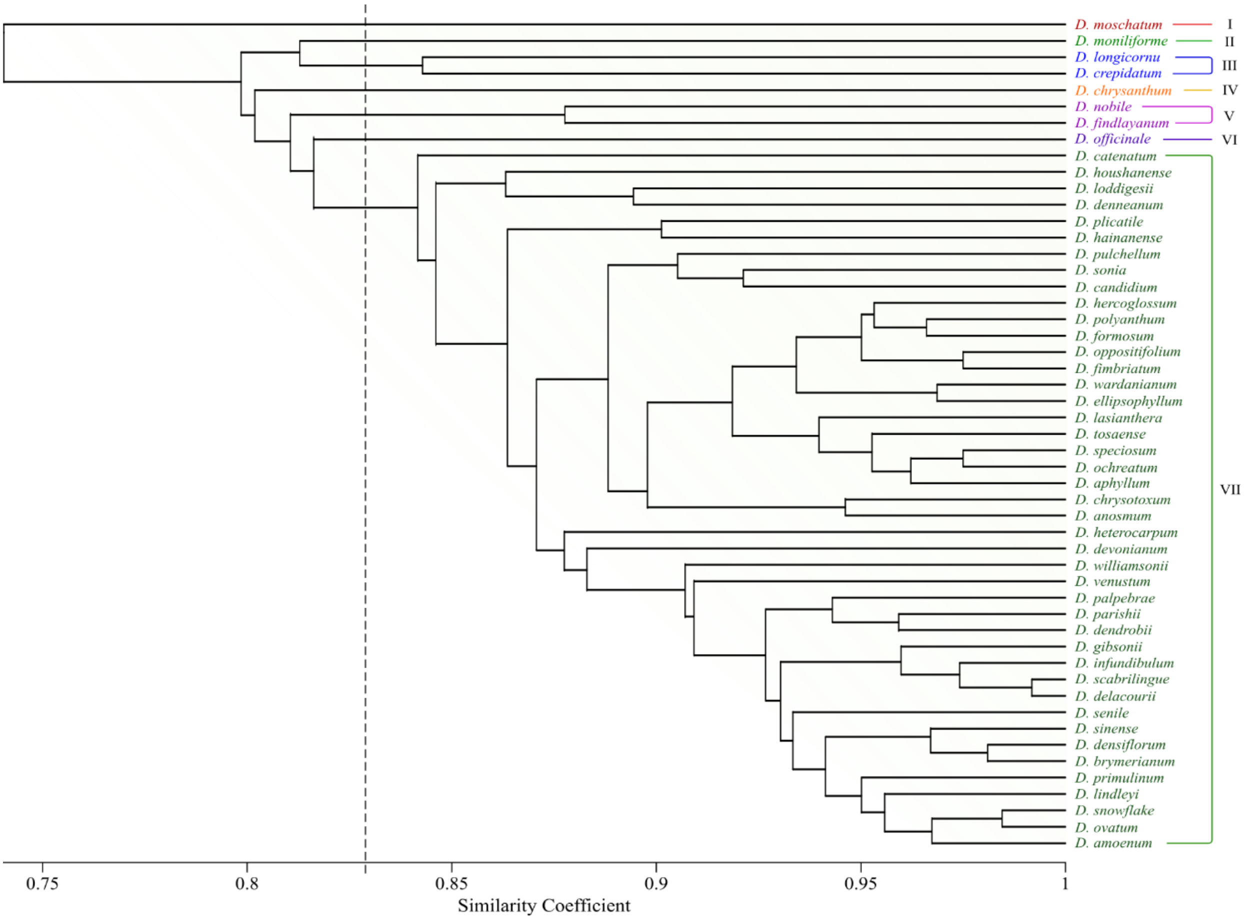

Figure 4. Dendrogram shows the genetic relationship of *Dendrobium* based on bioactive compounds and its bioactivities.

Based on a morphological marker, namely internode number (flowering shoot), *D. moschatum* had a close relationship with *D. secundum, D. chrysanthum*, and *D. aphyllum* (De et al., 2015). *Dendrobium aphyllum* alone had a close relationship with *D. loddigesii* following the ISSR marker

(Wang et al., 2009). Using four chloroplast markers, i.e., *mat*K, *rbc*L, *trn*L intron, and *trn*H-*psb*A, including the nuclear ribosomal DNA or the internal transcribed spacer (ITS), (Xiang et al., 2013) also reported the closed relationship between *D. loddigesii* and *D. aphyllum*. However, by the ITS and the SSR (simple sequence repeat), *D. moschatum* had to be closed with *D. denneanum* and *D. fimbriatum* (Yuan et al., 2009), including *D. heterocarpum* (Zhao et al., 2019). Finally, *D. moschatum* had a close relationship with *D. crumenatum*, *D. anosmum*, *D. macrophyllum*, and *D. spectabile* by chromosome number (2n = 38) (Zheng et al., 2018).

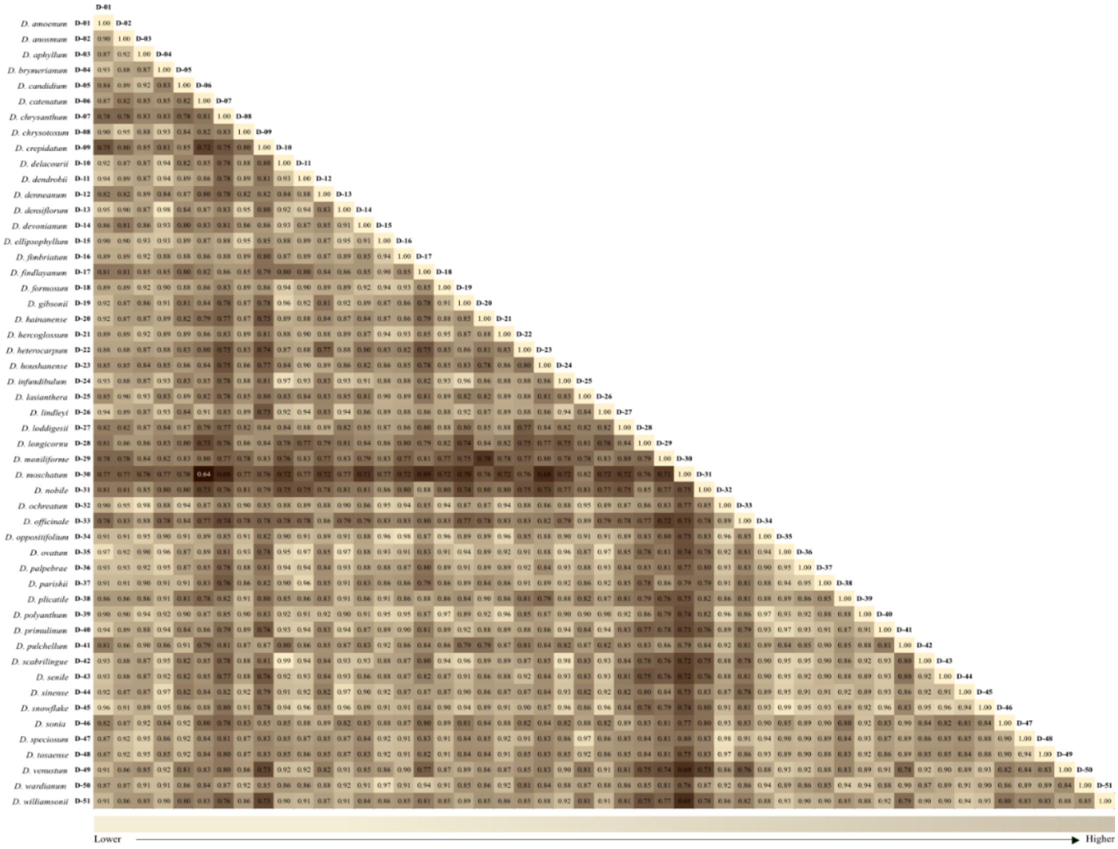

Figure 5. Genetic distance between *Dendrobium* species based on bioactive compounds and their bioactivities, revealed by maximum likelihood (ML).

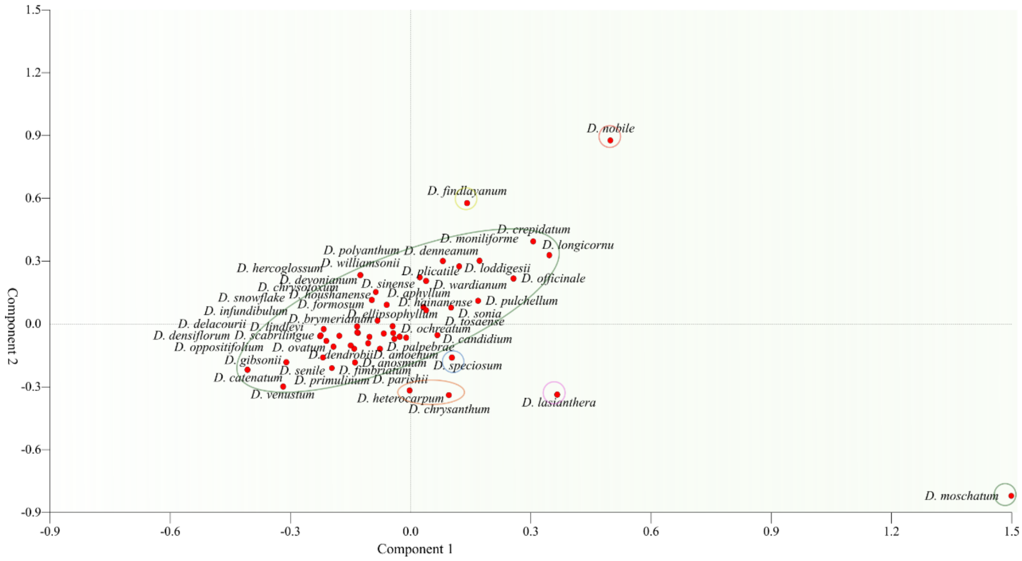

Figure 6. Grouping of *Dendrobium* based on bioactive compounds and their bioactivities, revealed by principle component analysis (PCA).

4. Conclusion

Based on bioactive compounds, their biological activities, and plant organs, *Dendrobium* shows unique genetic diversity and relationships. In this case, the highest genetic diversity was shown by polyphenols (H' index = 0.90) as substances, neuroprotective (H' = 0.80) for activity, and the leaf organ with an H' index of 0.89. The UPGMA analysis showed that *Dendrobium* grouped into seven clusters, where the furthest relationship was presented by *D. moschatum* and *D. catenatum*. Meanwhile, the closest relation was by *D. scabrilingue* with *D. delacourii*, including *D. snowflake* and *D. ovatum*. This information is valuable for future *Dendrobium* conservation and breeding programs.

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