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A systematic review of medicinal nickel hyperaccumulator plants in Southeast Asia: A phytochemical perspective

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ABSTRACT. Nickel (Ni) hyperaccumulators are unique plants that can accumulate high levels of Ni in their tissues without suffering from toxicity and garner attention due to their phytoremediation and ethnomedicine potentials. This study aimed to provide a list of Ni hyperaccumulators found in Southeast Asia, their geographic distribution, conservation status, phytochemistry, and medicinal properties based on research findings from various literatures and propose conservation measures for potential medical hallmarks. A systematic approach was employed by adhering to the Preferred Reporting Items for Systematic Items and Meta-Analyses (PRISMA) guidelines to gather data from various scientific sources, which resulted in the analysis of 55 Ni hyperaccumulators. The principal component analysis (PCA) was used to identify the correlation between the plant orders and the three components in which the positive and negative correlations exhibit the relationship of plant orders to the presence of medicinal plants, phytochemicals, and biological activities. The PCA revealed that Ericales (0.98), Malpighiales (0.95), and Myrtales (0.92) showed strong associations with medicinal properties and phytochemical diversity. Furthermore, the results indicated that 16 species (29%) possess documented medicinal properties, with the family Phyllanthaceae being particularly well-represented. Key phytochemicals such as alkaloids, flavonoids, and phenolics, known for their antimicrobial, antioxidant, and anti-diabetic properties, were identified. However, 39 species (71%) remained unexamined for medicinal efficacy, highlighting a critical research gap. This highlights the need for further exploration of the pharmaco-medical properties of unstudied species. To safeguard their ecological and medicinal value, conservation efforts need to be prioritized in ultramafic ecosystems, where these plants predominantly thrive. Ni hyperaccumulators hold significant therapeutic potential; therefore, further research is essential to uncover their medicinal applications and broaden their contributions to ethnomedicine and phytochemistry.

Keywords: antimicrobial, ethnomedicine, medicinal plants, metallophytes

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INTRODUCTION

Hyperaccumulator plants are uncommon plants known to thrive on metalliferous soils and accumulate extraordinarily high amounts of heavy metals in their above-ground living tissues, far more than the normal levels found in the majority of plant species without intoxicating themselves (Van der Ent, 2011; Fernando *et al*., 2013; Van der Ent *et al*., 2015; Reeves, 2024). While the presence of cadmium (Cd), zinc (Zn), and other metal accumulators impacted the grounds for sustainable biotechnologies, about 532 species are nickel (Ni) hyperaccumulators (Reeves, 2024; Reeves *et al*., 2018) and current knowledge and research on the overall mechanisms involved

Ni accumulation remain limited (Reeves, 2006; Jaffre' *et al*., 2013; Quimado *et al*., 2015; Van der Ent *et al*., 2016). Since the presence of this metal is naturally harmful to soil and many plants (Boyd, 2004; Seregin & Kozhevnikova, 2006; Brown, 2015), these hyperaccumulators have attracted attention due to their unique eco-physiological features that can be exploited in phytomining technology (He *et al*., 2012; Pollard *et al*., 2014).

Hyperaccumulators are found worldwide but are most common on landmasses with moderate, hot, and humid conditions (Proctor, 2003; Prasad, 2005; Gei *et al*., 2020). These hyperaccumulators are primarily found in New Caledonia, Cuba, Southeast Asia, Brazil, southern Europe, and Asia Minor for Ni; in northwest Europe for Zn and lead (Pb); and in south-central Africa for copper (Cu) and cobalt (Co). Among heavy metals, hyperaccumulator plants that are consistently restricted to metalliferous soils and show continuous hyperaccumulation of metals are called obligate hyperaccumulators. In contrast, species that hyperaccumulate from metalliferous soils but can also thrive on normal or non-metalliferous soils are called facultative hyperaccumulators (Pollard *et al*., 2014).

Hyperaccumulation is thought to have evolved to suppress competing plant species, a process known as natural allelopathy, or to defend against insect herbivores, referred to as elemental herbivory protection (Boyd & Jaffré, 2001; Van der Ent *et al*., 2015). Accordingly, hyperaccumulators increase Ni concentrations in the soil at the base of the plant due to leaf senescence and abscission, which may inhibit the growth and germination of competing plant species through poisoning (Boyd, 2004). Boyd (2012) proposed an alternative, claiming that the secondary theory, the Defensive Enhancement Hypothesis, emphasizes the protective role of foliar Ni concentrations against insect herbivores. It suggests that increased concentrations enhance plant health after an initial, low concentration of foliar Ni, leading to a stepwise accumulation of foliar Ni. Additionally, the Joint Effects Hypothesis suggests that Ni accumulation, in combination with natural compounds such as alkaloids, may have synergistic effects on hyperaccumulator plants (Boyd, 2012; Van der Ent *et al*., 2015).

The presence of heavy metals in medicinal plants may promote the development of bioactive substances. Different plant species exhibit varying responses to metals, highlighting the need to select the appropriate medicinal plant when managing metal contamination and soil toxicity. This suggests the need for investigations to determine the type and concentration of heavy metals in each medicinal plant (Maleki *et al*., 2017).

Some Ni hyperaccumulators exhibit promising medicinal properties and have been used in traditional medicine for centuries. Heavy metals may play a significant role in influencing plant genes to alter the production of secondary metabolites (Kabera *et al*., 2014; Wink, 2015). Specifically, the reactive oxygen species (ROS) produced during heavy metal stress may cause lipid peroxidation, promoting the formation of highly active signaling compounds (Nasim & Dhir, 2010). This study used data from published studies within the region to compile a comprehensive list of Ni hyperaccumulator plants with medicinal properties in Southeast Asia. Specifically, this study aimed to: 1) compile a list of Ni hyperaccumulator plants found in Southeast Asia's ultramafic forests with reported medicinal uses, 2) list the phytochemical composition and medicinal properties of Ni hyperaccumulator plants based on existing research, and 3) identify Ni hyperaccumulators with potential medicinal properties.

METHODOLOGY

This study employed various techniques to gather data on Ni hyperaccumulator plants found in the ultramafic forests of Southeast Asia and their respective medicinal properties based on published journals and related studies concerning their therapeutic applications for various conditions and illnesses.

Eligibility criteria

The Patient-Intervention-Comparison-Outcome (PICO) approach was used to detail research questions and keywords (Santos *et al*., 2007), following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.,* 2015), to evaluate the literature gathered from online sources systematically.

Information sources

Manual searches of relevant peer-reviewed literature were conducted using the online databases PubMed, Google Scholar, and ScienceDirect. PDF copies of articles unavailable in one database or another were also obtained.

The formulation of search terms aligned with this systematic review's research question and objectives, using the PICO approach, and considered all articles published between 2000 and 2020. The keywords "serpentine geoecology," "nickel hyperaccumulators," and ''ultramafic phytochemistry'' were used in this study.

Inclusion and exclusion criteria

Article titles were manually screened to exclude studies not related to the subject. Only vascular plants were included in the study, and relevant articles were meticulously inspected to determine their fit with the eligibility criteria of this systematic review. The inclusion criteria were as follows: 1) validated sources of material related to plants identified to the taxonomic levels of order, genus, and species; 2) research that focused on Ni hyperaccumulators found in Southeast Asia; 3) research published between 2000 and 2020; and 4) availability of the full-text article in English. Articles published in non-English languages and those not open access were excluded.

Selection process

The identification and screening process for the systematic review is outlined in the methodological framework (**Figure 1**). The literature search yielded 23,892 articles, of which 14,452 were extracted, resulting in 9,440 for inclusion. Additionally, general criteria such as the date range (2000–2020) and full-text availability removed 4,889 articles. Specific criteria such as topic relevance, English language, and focus on plants in Southeast Asia were then applied, excluding 4,486 articles, leaving 65 articles included in this systematic review.

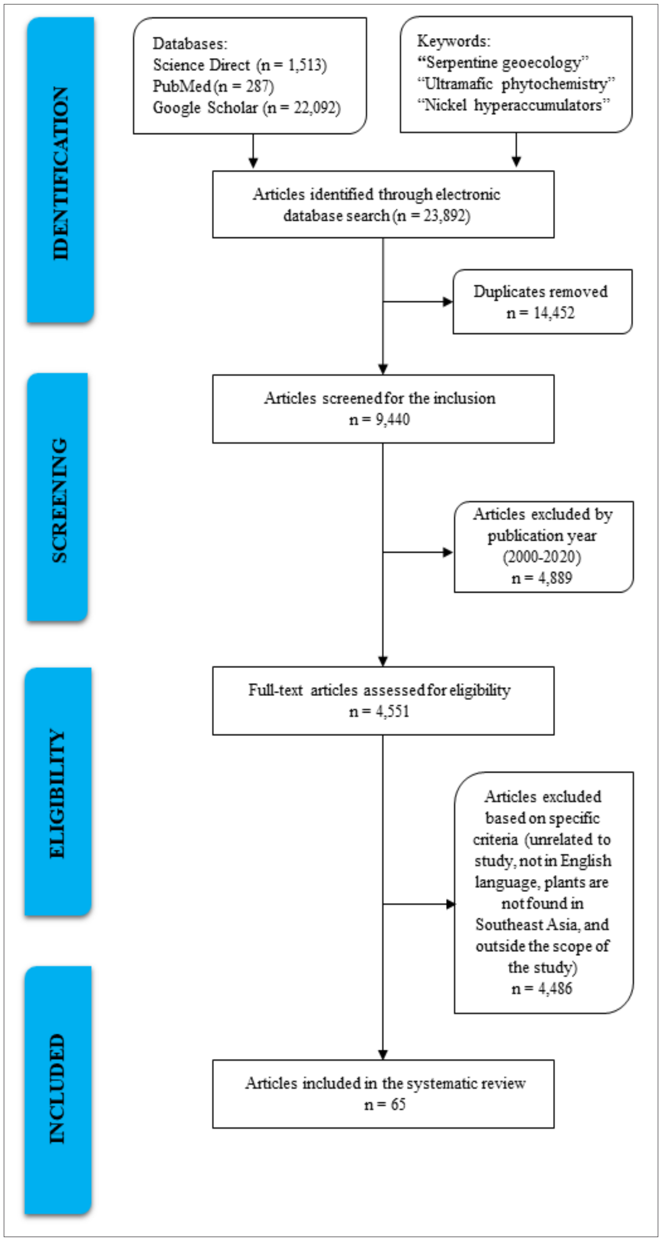

Figure 1. Representation of inclusion and exclusion criteria, with corresponding results from the literature search used to construct the databases.

Plant terminology

All identified plant names were cross-referenced for accuracy using the World Plants: Complete Plant List (https://www.worldplants.de/world-plants-complete-list/) and the World Checklist of Selected Plant Families (https://wcsp.science.kew.org/). The conservation status of Ni hyperaccumulator plants in this study was verified using the IUCN Red List of Threatened Species (https://www.iucnredlist.

org/species/) and DAO 2017–11, particularly for plants in the Philippines.

Data extraction

Data for this research were tabulated in **Table 1**. Whenever requested by the author, information on data gathering and extraction procedures for medicinal applications was systematically included in the research material. Microsoft Excel was used for data analysis and statistical treatment to ensure transparency in methodological procedures and minimize study bias.

Data analysis

Statistical analysis was performed on the data and attributes of plant orders. Information obtained from the literature search was organized and analyzed using Microsoft Excel. The attributes of plant orders were further examined using Principal Component Analysis (PCA) via the ClustVis tool (Metsalu & Vilo, 2015). The PCA was applied to determine the strength of relationships among the variables, with correlation coefficients used to assess these relationships (Akoglu, 2018). The analyzed data included the number of plant species, the number of medicinal plants, and the number of phytochemicals associated with each plant order.

RESULTS

Taxonomic and geographic distribution of nickel hyperaccumulator plants in Southeast Asia with reported medicinal uses

Figure 2 presents this study's distribution of Ni hyperaccumulator species across 20 plant families. The Phyllanthaceae Family contains the 20 most significant number of species. Ochnaceae and Violaceae have four species, while Myrtaceae, Rubiaceae, and Salicaceae have three species. Families such as Lamiaceae, Meliaceae, Myristicaceae, and Sapotaceae were represented by two species each. In contrast, Acanthaceae, Anacardiaceae, Chrysobalanaceae, Dipterocarpaceae, Dichapetalaceae, Fabaceae, Monimiaceae, Oxalidaceae, Sapindaceae, and Tiliaceae were each represented by a single species. Additionally, the phylogenetic relationships among angiosperm orders, focusing on the number of medicinal plants identified in the specific orders were included in the study (**Figure 3**). The Malphigiales order has the highest representation, with 7 medicinal plants, followed by Gentianales with 3 species, and Sapindales with 2 species. The orders Ericales, Fabales, Magnoliales, and Myrtales each include one medicinal species. These counts are represented as bar graphs above the corresponding branches on the phylogenetic tree, indicating the distribution of medicinal plant species across the key plant orders.

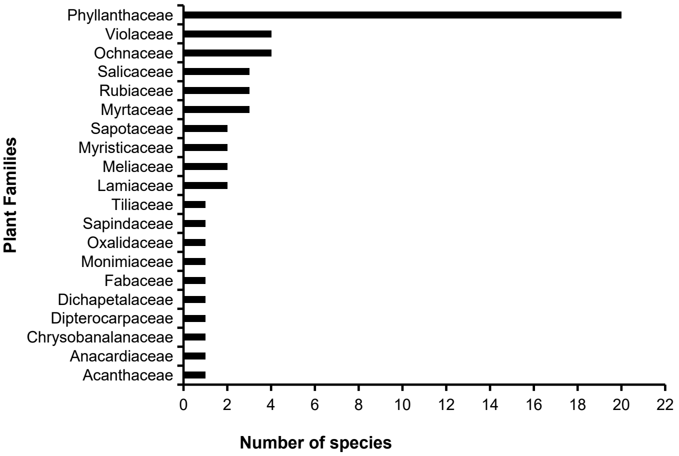

Figure 2. Number of nickel hyperaccumulator plant species per family included in the elucidation of phytochemical and medicinal properties in this study.

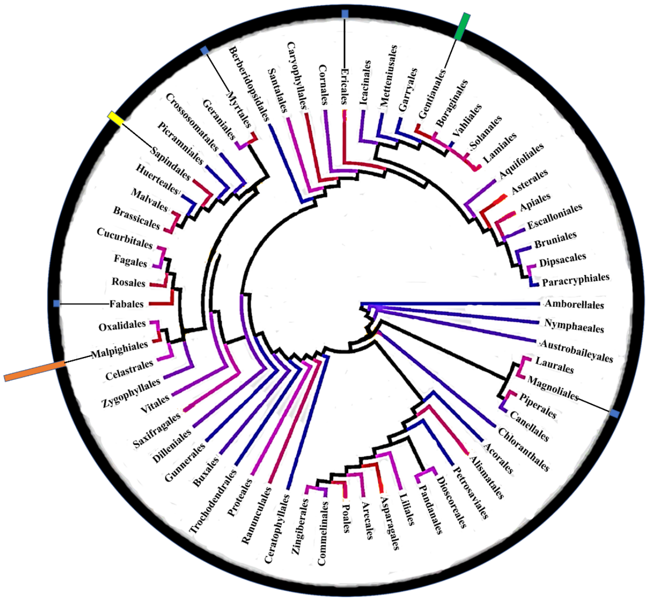

Figure 3. Ordinal-level angiosperm phylogeny of plant orders (figure borrowed with direct permission from Soltis *et al*., 2019, in line with Angiosperm Phylogeny Group, 2016).

Notably, the medicinal plants at the top of the phylogenetic tree, represented by bar graphs, are distributed across 10 families — namely the Sapotaceae (Order Ericales), Fabaceae (Fabales), Rubiaceae (Gentianales), Myristicaceae (Magnoliales), Dichapetalaceae, Phyllanthaceae, Violaceae (all from Malphigiales), Myrtaceae (Myrtales), and the Meliaceae and Sapindaceae (Sapindales).

Figure 4 illustrates the number of Ni hyperaccumulator plant families across Southeast Asia. The number of plant families containing Ni hyperaccumulator species varies across regions, with Malaysia having the highest representation (14 families), followed by the Philippines (13 families), and Laos having the lowest (4 families).

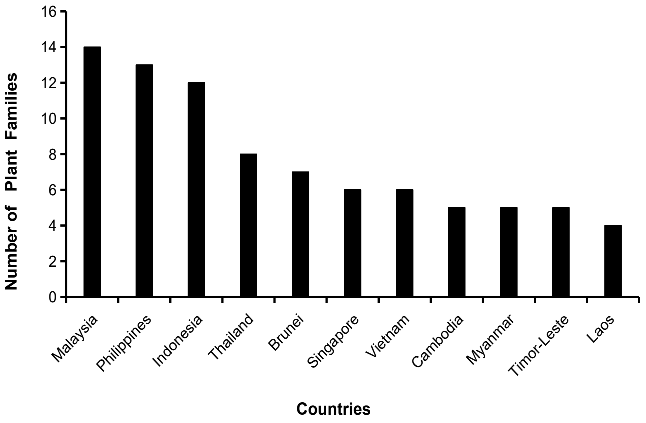

Figure 4. Number of nickel (Ni) hyperaccumulator plant families in SE Asian countries.

Principal component analysis of medicinal plant orders based on biological and phytochemical profiles

The heatmap (**Figure 5**) provides insights into how different plant orders relate to three principal components (PC 1, PC 2, and PC 3) based on the presence of medicinal plants, number of phytochemicals, and number of biological activities. The PC 1, which captures the most variance at 65%, shows strong positive correlations with Ericales (0.98), Malpighiales (0.95), and Myrtales (0.92), indicating that these orders are more strongly associated with medicinal properties, a greater variety of phytochemicals, and diverse biological activities. In contrast, plant orders like Magnoliales and Sapindales have weaker correlations with PC 1, suggesting a lesser influence on these attributes.

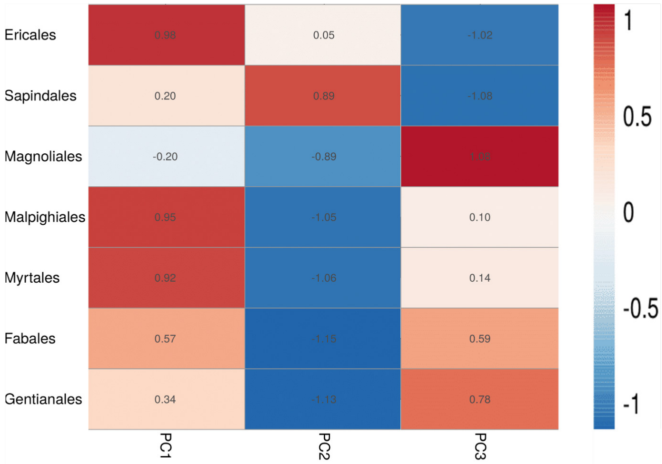

Figure 5. Heatmap of PCA loadings showing the correlations between plant orders and the three principal components.

The PC 2, which explains 35% of the variance, has a high positive correlation with Sapindales (0.89) but strong negative correlations with Fabales (–1.15) and Myrtales (–1.06), highlighting distinct relationships between these plant orders and the medicinal characteristics. Although PC 3 contributes minimally, it shows a notable positive correlation with Magnoliales (1.08) and moderate associations with Gentianales (0.78) and Fabales (0.59). The color gradient from blue to red represents the direction and correlation strength, where red indicates positive, and blue indicates negative associations. Overall, this analysis points to Ericales and Malpighiales as key orders with stronger links to medicinal properties and phytochemical diversity in the data.

Medicinal potential of nickel hyperaccumulator plants

Of the 55 Ni hyperaccumulator plants found in Southeast Asian vegetation, 16 species (29.09%) have been reported to exhibit medicinal activities. **Table 1** summarizes the medicinal properties, extraction methods, active compounds, and specific plant tissues used for various Ni hyperaccumulator plants in Southeast Asia. Traditional preparations for these plants often involve techniques such as methanol extraction, to treat respiratory, gastrointestinal, and skin ailments, inflammation, diabetes, and oxidative stress. Certain plants display distinct medicinal traits, such as *Psychotria* species, commonly used for respiratory and digestive issues, and *Walsura pinnata*, which contains compounds with potential anti-cancer properties.

Moreover, key bioactive compounds identified include triterpenoids, flavonoids, phenolics, tannins, alkaloids, lignans, saponins, steroids, and coumarins, with flavonoids frequently appearing across multiple species for their antioxidant and anti-inflammatory effects. The medicinal use of plant parts varies by species, with roots, leaves, bark, fruits, and whole plants utilized. For instance, the roots of *Dichapetalum geloniodes* and the bark of *W. pinnata* are processed specifically for their medicinal properties. Nevertheless, certain species, such as *Mischocarpus sundaicus* and *Rinorea javanica*, lack comprehensive phytochemical profiles, highlighting an important area for further study.

Table 1. Ni hyperaccumulator plants of Southeast Asia with reported medicinal properties, plant part used, and active secondary metabolites.

Species	Extract	Medicinal use	Secondary metabolite	Plant tissue
Dichapetalum geloniodes ssp. *tuberculatum*	Simple maceration	Jing *et al.* (2014) pointed out that the plant's dichapetalin hybrid triterpenoids have a wide range of physiologically active cellular activities, including protection against infections.	Triterpenoids	Root
Dalbergia beccarii	Methanol extract	Different species are frequently used to treat a variety of illnesses, including aphthae, bleeding piles, cough, diarrhea, dysentery, dyspepsia, epigastria, epistaxis, gonorrhea, hemorrhages, leprosy, malaria, rheumatism, scabies, scalding urine, stomachache, syphilis, traumatic injuries, and ulcers (Saha *et al*., 2013).	Flavonoids, phenolics	Entire plant
Walsura pinnata	Simple maceration	Phytochemical study on bark has led to the isolation of a new oleanane triterpene acid, 3-oxo-olean-9(11),12-dien-28-oic acid, and nine other compounds. Compounds 3 and 4 showed in vitro growth inhibitory activity against two human cancer cells MCF-7 and SK-OV-3 (Mahdzir *et al*., 2017).	Terpenoids	Bark
Knema matanensis	Methanol extract	Some *Knema* species are used medicinally, with the seeds and bark being used in traditional medicine to treat disorders affecting the skin or ulcers in the mouth and throat (Salleh & Ahmad, 2017).	Flavonoids,lignans, phenolics	Bark Seed
Syzygium sp.	Methanol extract	*Syzygium* species are medicinal plants utilized in herbal medicine for centuries because of their anti-cardiometabolic qualities (Chagas *et al*., 2015).	Alkaloids, flavonoids	Entire plant
Baccaurea lanceolata	Methanol	It is known for its antioxidant activity and is used to treat stomachache and swellings in the body (Lim, 2012; Abu Bakar *et al*., 2014).	Flavonoids, phenols	Fruit Leaf
Breynia cernua	Methanol extract	*Breynia cernua* leaves have been used in various ways, either directly or prepared, to help alleviate ailments like cough, sore throat, ulcers, and fever (Azzam *et al*., 2022)	Alkaloids, flavonoids, phenols, saponins, tannins	Entire plant

Table 1. *Con't.*

Species	Extract	Medicinal use	Secondary metabolite	Plant tissue
Glochidion arborescens	Methanol extract Ethyl acetate extract	*Glochidion arborescens* has high antioxidant activity, and flavonoids are one of the secondary metabolites that might be used as antioxidants (Rahmiyani & Fitriyana, 2020).	Flavonoids	Entire plant
Glochidion rubrum	Methanol extract Ethanolic extract	Macerated leaves are used in the treatment of hemorrhoids (Stuart, 2020)	Lignans, tannins	Leaf
Glochidion cf. *sericeum*	Water extract	Biological activity tests revealed that the leaves have anti-diabetic and anti-cholesterol properties (Hadi & Waluyo, 2020).	Alkaloids, flavonoids, saponins, steroids, tannins	Leaf
Psychotria cf. *gracilis*	Methanol extract	In traditional medicine, *Psychotria* plants are often used to treat bronchial and gastrointestinal conditions like cough, bronchitis, ulcers, and stomachaches (Calixto *et al*., 2016).	Alkaloids, coumarins, flavonoids, terpenoids, tannins	Entire plant
Psychotria sp.	Methanol extract	*Psychotria* plants (leaves, roots, bark, and rhizomes) are extensively used in traditional medicine to treat bronchial and gastrointestinal ailments like cough, bronchitis, ulcers, and stomachaches (Calixto *et al*., 2016).	Alkaloids, coumarins, flavonoids, terpenoids, tannins	Entire plant
Psychotria sarmentosa	Aqueous extract	Powerful pain-relieving and additionally calming action (Jayantha *et al*., 2022).	Flavonoids, tannins	Leaf
Mischocarpus sundaicus	No phytochemical data	A decoction of the roots is used medicinally against coughs (Fern, n.d.).	No phytochemical data	Root
Planchonella obovata	Ethanol extract	An ethanol extract of the leaf of *Planchonella obovata*, one of two *Planchonella* species found in Taiwan, demonstrated inhibitory efficacy against the HL-60 leukemia cell line, which causes acute promyelocytic leukemia (APL), according to preliminary testing as per Chen *et al.* (2015).	Triterpenoids	Leaf
Rinorea javanica	No phytochemical data	In Java, squashed leaves of *Rinorea javanica* (Blume) O. Kuntze have been directed inside as an antitoxin (PROSEA, n.d.)	No phytochemical data	Leaf

Table 2, on the other hand, shows a comprehensive list of Ni hyperaccumulators with no reported medicinal properties. The term "no reported" is emphasized to indicate that the lack of reported medicinal properties is due to circumstances, including information gaps in the existing literature. For this case, **Table 2** provides an overview of various Ni hyperaccumulator plant species from different families, highlighting their Ni concentration levels and geographic distribution across Southeast Asia and nearby regions. Notably, Phyllanthaceae has the largest representation, with several high-accumulating species such as *Actephila* sp., *Emblica erythrotricha*, and *Dendrophyllanthus securinegoides* which are found in areas like Borneo, the Philippines, and Sabah. Moreover, Violaceae includes prominent hyperaccumulators like *R. niccolifera*, native to the Philippines, and *R. bengalensis*, which is distributed throughout Southeast Asia and Australia.

Other families with notable hyperaccumulator species include Chrysobalanaceae, with *Licania splendens* in the Philippines, Malaysia, and Indonesia, and Sapotaceae, represented by *Planchonella oxyedra* in Indonesia. Conservation statuses of these species vary, ranging from endangered, such as those of *Shorea tenuiramulosa* (Dipterocarpaceae) and *R. niccolifera* (Violaceae) to not evaluated. This data highlights Ni hyperaccumulator plants' widespread presence and ecological diversity in tropical regions, emphasizing their unique adaptations to metal-rich soils and the importance of conservation efforts.

Table 2. Ni hyperaccumulator plants in Southeast Asia with no reported medicinal properties (with reference to Galey *et al*., 2017).

Family	Scientific name	Nickel hyper-accumulation amount (ppm)	Distribution	Conservation status	Reference
Acanthaceae	*Ptyssiglottis fusca*	1,160	Sabah	Not evaluated	Van der Ent *et al.* (2015)
Anacardiaceae	*Buchanania microphylla*	---	Philippines and China	Not evaluated	Ata *et al.* (2016)
Chrysobalanaceae	*Licania splendens*	3,409	Philippines; Malaysia; Indonesia	Least concern (IUCN)	Fernando *et al*. (2013)
Dipterocarpaceae	*Shorea tenuiramulosa*	1,790	NE-Borneo (Sabah)	Endangered (IUCN)	Van der Ent *et al.* (2015)
Lamiaceae	*Callicarpa micrantha*	---	Philippines, Northern Marianas, Palau, Fed. States of Micronesia	Not evaluated	Ata *et al.* (2016)
Lamiaceae	*Callicarpa* sp.	1,383	Philippines, Northern Marianas, Palau, Fed. States of Micronesia	Not evaluated	Fernando *et al*. (2013)
Meliaceae	*Walsura monophylla*	7,090	Malaysia, Philippines	Endangered (IUCN)	Baker *et al.* (1992)
Monimiaceae	*Kibara coriacea*	5,840	Southeast Asia	Least concern (IUCN)	Van der Ent *et al.* (2015)
Myristicaceae	*Myristica laurifolia* var. *bifurcata*	1,100	Indonesia	Not evaluated	Wither & Brooks (1977)
Myrtaceae	*Decaspermum blancoi*	3,841	Philippines (Luzon, Sibuyan)	Not evaluated	Fernando *et al*. (2013)
Myrtaceae	*Decaspermum vitis-idaea*	---	Borneo, Philippines (Mindanao)	Least concern (IUCN)	Ata *et al.* (2016)
Ochnaceae	*Brackenridgea palustris* ssp. *foxworthyi*	7,600	Philippines	Not evaluated	Baker *et al.* (1992)
Ochnaceae	*Brackenridgea palustris* ssp. *kjellbergii*	1,440	Sulawesi	Not evaluated	Reeves (2003)
Ochnaceae	*Brackenridgea fascicularis*	4,488	Philippines	Least concern (LC)	Van der Ent *et al.* (2015)
Ochnaceae	*Brackenridgea mindanaensis*	---	Mindanao, Philippines	Not evaluated	Fernando *et al.* (2020)
Oxalidaceae	*Sarcotheca celebica*	---	Indonesia	Not evaluated	Van der Ent *et al.* (2013)
Phyllanthaceae	*Actephila alanbakeri*	1,790		Not evaluated	Van der Ent *et al.* (2015)
Phyllanthaceae	*Actephila* sp.	11,520	Sabah	Not evaluated	Van der Ent *et al.* (2015)
Phyllanthaceae	*Aporosa chalarocarpa*	1,560	Malaysia	Not evaluated	Van der Ent *et al.* (2015)
Phyllanthaceae	*Cleistanthus* sp. 1	2,110	Bidu-Bidu Hills	Not evaluated	Van der Ent *et al.* (2015)
Phyllanthaceae	*Nymphanthus balgooyi*	8,610	Palawan; Borneo (Sabah)	Vulnerable (DAO 2017-11)	Hoffmann *et al*. (2003); Quimado *et al* (2015)
Phyllanthaceae	*Glochidion* aff. *acustylum*	6,060	Sulawesi	Not evaluated	Reeves (2003)
Phyllanthaceae	*Glochidion brunneum*	6,200	Southeast Asia	Not evaluated	Van der Ent *et al.* (2015)

Table 2. *Con't.*

Family	Scientific name	Nickel hyper-accumulation amount (ppm)	Distribution	Conservation status	Reference
Phyllanthaceae	*Glochidion* cf. *lanceisepalum*	3,270	Borneo (Sabah)	Not evaluated	Van der Ent *et al.* (2015)
Phyllanthaceae	*Glochidion* cf. *mindorense*	2,280	Southeast Asia	Data deficient (IUCN)	Van der Ent *et al.* (2015)
Phyllanthaceae	*Glochidion* sp. *"panantaran"*	2,893	Sabah	Not evaluated	Van der Ent *et al.* (2015)
Phyllanthaceae	*Emblica rufuschaneyi*	16,490	Borneo (Sabah)	Endangered (IUCN)	Bouman *et al*., (2018)
Phyllanthaceae	*Emblica erythrotricha*	18,492	Philippines (Luzon, Sibuyan, Mindanao)	Not evaluated	Quimado *et al.* (2015)
Phyllanthaceae	*Dendrophyllanthus securinegoides*	23,300	Borneo (Sabah) and Philippines (Surigao)	Not evaluated	Quimado *et al.* (2015); Van der Ent *et al.* (2015)
Phyllanthaceae	*Glochidion* sp. *'bambangan'*	16,700	Borneo (Sabah)	Not evaluated	Van der Ent *et al.* (2015)
Phyllanthaceae	*Glochidion* sp. *'nalumad'*	9,000	Borneo (Sabah)	Not evaluated	Van der Ent *et al.* (2015)
Salicaceae	*Flacourtia kinabaluensis*	7,280	Sabah	Least concern (IUCN)	Van der Ent *et al.* (2015)
Salicaceae	*Scolopia luzonensis*	---	Philippines, Borneo, Sulawesi	Not evaluated	Van der Ent *et al.* (2019)
Salicaceae	*Xylosma luzonensis*	5,360	Philippines, Indonesia, Lesser Sunda Isl.	Other threatened Species (DAO 2017-11)	Van der Ent *et al.* (2015)
Sapotaceae	*Planchonella oxyedra*	19,600	Obi Island, Indonesia	Not evaluated	Wither & Brooks (1977)
Tiliaceae	*Trichospermum kjellbergii*	3,770	Indonesia	Not evaluated	Wither & Brooks (1977)
Violaceae	*Rinorea bengalensis*	12,800	Southeast Asia and Australia	Not evaluated	Van der Ent *et al.* (2015)
Violaceae	*Rinorea niccolifera*	18,000	Philippines	Endangered (DAO 2017-11)	Fernando *et al.* (2014)
Violaceae	*Rinorea* sp. indet.	1,830	Sabah	Not evaluated	Proctor *et al.* (1994)

Phytochemical composition of medicinal nickel hyperaccumulator plants

Figure 6 provides an overview of secondary metabolites identified in Ni hyperaccumulator plants with medicinal uses. Flavonoids are the most prevalent, detected in 10 species, followed by tannins in 6 species, and alkaloids in 5. Other compounds, such as phenols, terpenoids, triterpenoids, saponins, lignans, steroids, and coumarins, are less common in regard to triterpenoids, lignans, and coumarins that appear in only two species. Additionally, three species lack specific phytochemical data, suggesting potential areas for future study.

Biological activities of medicinal nickel hyperaccumulator plants

Figure 7 details the biological activities associated with medicinal Ni hyperaccumulator plants. Among these, antimicrobial effects are the most commonly identified in 10 species, while analgesic effects are seen in 6 species. Anti-inflammatory and antioxidant activities are found in 5 species. Additionally, antipyretic, hepatoprotective, and antidiabetic effects are reported in two species. On an important note, some plants exhibit rarer activities, including anticancer, anti-cholesterol, anti-hemorrhoidal, antitoxin, and antitussive properties, while two species have no recorded data on their biological activities.

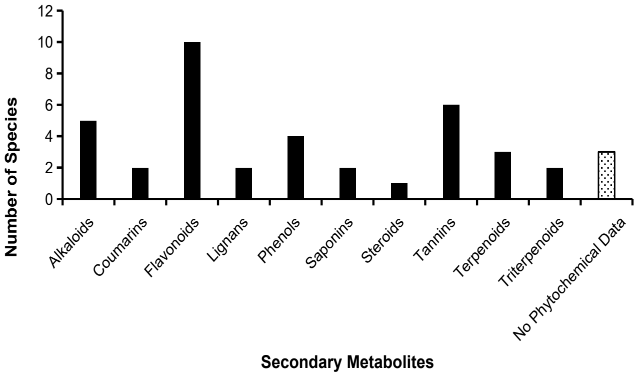

Figure 6. Secondary metabolites identified in Ni hyperaccumulator plant species with reported medicinal properties.

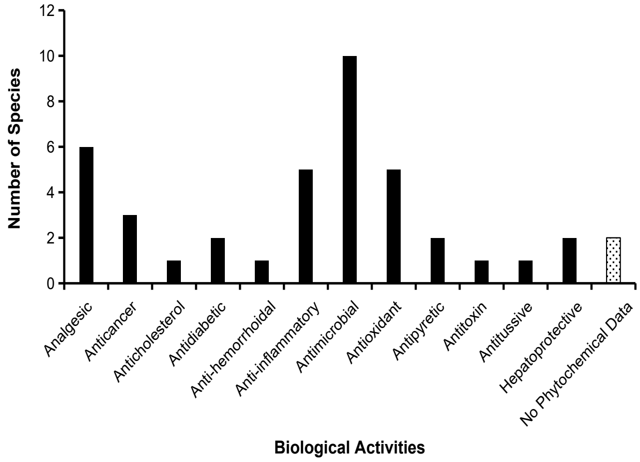

Figure 7. Biological activities of Ni hyperaccumulator plants with reported medicinal properties.

Conservation status of nickel hyperaccumulator plants in Southeast Asia

The conservation status assessment (**Figure 8**) of Ni hyperaccumulator plants in Southeast Asia, as classified by the IUCN Red List and DAO 2017–11, shows that most species have yet to be assessed, with 38 listed as not evaluated. Among those evaluated, 8 species are categorized as least concern on the IUCN Red List, while others face different threat levels, with three species marked as endangered and another three as vulnerable. One species is labeled as data deficient by the IUCN, while DAO 2017–11 identifies one species as critically endangered and another as other threatened species.

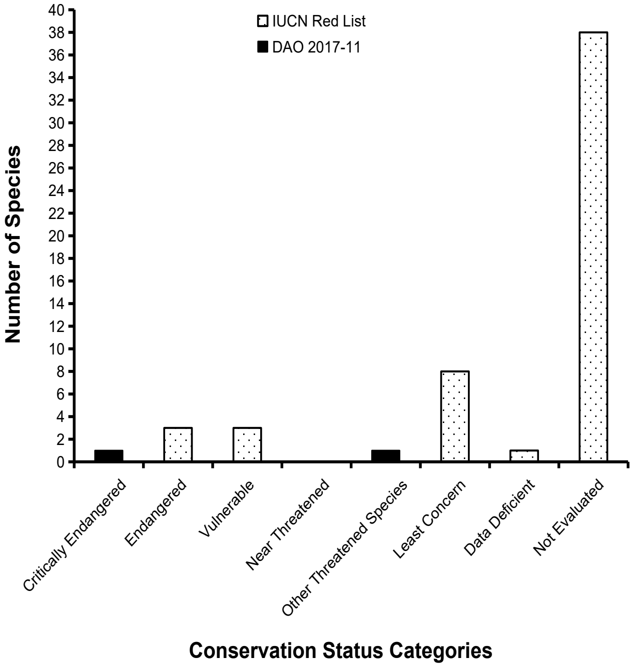

Figure 8. Conservation status of all nickel (Ni) hyperaccumulator plants identified in Southeast Asia.

DISCUSSION

Phylogenetic insights into nickel hyperaccumulators lacking reported medicinal properties

Some Ni hyperaccumulators in Southeast Asia have yet to be reported to have medicinal properties, possibly due to a lack of published research or limited investigation into their therapeutic potential concerning their safety and efficacy. Phylogenetic analysis offers a valuable method for exploring the medicinal qualities of plants by studying their evolutionary history and comparing properties based on their phylogenetic relationships. This approach involves constructing evolutionary trees to trace species' historical connections, helping identify patterns of medicinal use that may arise from shared ancestry. For example, related plants often exhibit similar biochemical characteristics and potential therapeutic properties due to their common evolutionary origin; several kinds of literature have shown how phylogenetic techniques can uncover clusters of plants with medicinal value that serve as a foundation for identifying species that may warrant further study. Studies by Zaman *et al*. (2022) and

Teixido-Toneu *et al*. (2018) highlight how these methods are applied to plant families like Lamiaceae to investigate medicinal uses, in which two species in this study from Lamiaceae – *Callicarpa* sp. and *Callicarpa micrantha* – are Ni hyperaccumulators with no reported medicinal properties and yet they could benefit from a deeper phylogenetic analysis to explore potential medicinal applications. This highlighted the effectiveness of the phylogenetic approach in analyzing the phytochemistry of closely related medicinal plant species with similar biochemical properties (Prinzing *et al*., 2001; Paton *et al*., 2004; Sharma & Sarkar, 2013; Munjal *et al*., 2019).

Additionally, phylogeny can predict potential therapeutic plants, particularly in plant families with no reported medicinal values. Phylogenetic analysis has proven effective in identifying promising pharmaceuticals within genera such as Pterocarpus and Narcissus, where evolutionary history is closely linked to therapeutic efficacy (Rønsted *et al*., 2008; Saslis-Lagoudakis *et al*., 2011). By applying similar phylogenetic methods to Ni hyperaccumulators in Southeast Asia, it may be possible to identify species with hidden medicinal properties, which can pave the way for future research into their safety, effectiveness, and potential pharmaco-medical applications.

Exploring medicinal potential in nickel hyperaccumulator plants

The influence of secondary metabolites and biological activities on the medicinal applications of hyperaccumulator plants are of great significance in botanical medicine, leading to numerous investigations into the pharmacology and phytochemistry of key plant species used for medicinal purposes. Notably, plants have long been regarded as a source of bioactive compounds with therapeutic properties and have been used to treat a variety of illnesses, including asthma, gastro-gastrointestinal issues, skin disorders, respiratory and urinary complications, and hepatic and cardiovascular diseases (Cousins & Huffman, 2002; Tian *et al*., 2014). The demand for plant-derived drugs, often considered safer than synthetic drugs, is rapidly growing. Based on the PCA of plant orders, considering the presence of medicinal plants, the number of phytochemicals, and the number of biological activities successfully reveals interesting relationship patterns. The PC 1 showed a strong correlation with the plant orders Ericales, Malpighiales, and Myrtales, which suggest that these orders play a significant role in the presence of medicinal properties, a greater variety of phytochemicals, and a higher number of biological activities. The substantial positive loadings for these orders indicate their critical importance in shaping the dataset's medicinal potential and phytochemical diversity. More importantly, these findings aligned with prior research that has emphasized the medicinal value and diverse bioactivity of species within these orders, such as Ericales and Myrtales, known for their antimicrobial effects, specifically in gram-positive and gram-negative bacteria, respectively (Pauw & Eloff, 2014). On the contrary, the lower correlations for Magnoliales and Sapindales with PC 1 implied that these plant orders contribute less to the medicinal attributes and phytochemical richness observed in the dataset and may suggest that although species in these orders do have medicinal potential, specifically the Sapindales as highlighted in the study of Tölke *et al*. (2022), they may not possess as diverse or abundant phytochemical profiles or biological activities as other plant orders.

For PC 2, which explained 35% of the variance, this presents an alternative pattern in which the positive correlation for Sapindales indicates that species from this order may exhibit distinct medicinal characteristics, particularly regarding phytochemical content. On the other hand, the negative loadings for Fabales and Myrtales suggest that these plant orders may not be as closely associated with medicinal properties, which indicates differences in the types of secondary metabolites and biological activities they exhibit, as highlighted in the study of Jadhavar & Deshpande (2022) which centralizes the variety of secondary metabolites in Fabaceae. Although the PC 3 explained no portion of the variance, it may still provide valuable insights. For example, the positive correlations observed for Magnoliales and Gentianales suggest that while these orders may not contribute significantly to the overall medicinal and phytochemical profiles, certain species within these groups could still offer important bioactive compounds. In the case of Gentianales, a study by Jensen & Schripsema (2002), the Gentianaceae family has been widely used in traditional medicine and contains promising compounds such as xanthones, iridoids, and C-glucoflavonoids. This was also supported in the study of Šiler & Mišić (2016), which focused on the bioactive compounds of the genus *Centaurium* under the Gentianaceae Family. The moderate positive loading for Fabales in PC 3 further highlighted the complexity of the relationship between plant orders and their medicinal properties due to the unique attributes possessed by various species (Gurib-Fakim, 2006).

Role and significance of secondary metabolites in medicinal nickel hyperaccumulator plants

Secondary metabolites (SMs) are a diverse group of compounds produced by plants that play significant roles in plant defense, survival, and adaptation which are increasingly recognized for their broad range of medicinal properties, including antimicrobial, antioxidant, anti-inflammatory, analgesic, and anticancer activities, making them valuable in human health and agriculture (Rang *et al*., 2011; Vaishnav & Demain, 2011; Kliebenstein, 2013; Thirumurugan *et al*., 2018; Yang *et al*., 2018; Hussein & El-Anssary, 2019). The findings regarding the Ni hyperaccumulator's phytochemical compositions and biological activities highlighted the importance of secondary metabolites in their medicinal properties.

As shown in the result of the phytochemical composition of medicinal Ni hyperaccumulators, the most prevalent secondary metabolites are flavonoids, tannins, and alkaloids detected in multiple species and known for their significant medicinal properties. Flavonoids, for example, have demonstrated antioxidant, anticancer, and anti-inflammatory effects (Robertson, 2021), consistent with the biological activities of medicinal Ni hyperaccumulators shown in the results, where antioxidant and anti-inflammatory effects were identified in several species. Similarly, tannins and alkaloids have been associated with antimicrobial and analgesic properties (Kurek, 2019; Singh & Kumar, 2020), further supporting the medicinal potential of these plants.

Flavonoids are essential in the context of medicinal plants due to their broad biological activities. These compounds are commonly found in plants, where they serve as pigments to attract pollinators and act as defense agents against pathogens (Ullah *et al*., 2020). The prevalence of flavonoids in 10 species of Ni hyperaccumulators in the study aligns with the antimicrobial and anti-inflammatory activities highlighted in the biological activities of medicinal Ni hyperaccumulators, reinforcing their crucial role in plant defense and medicinal efficacy. Moreover, tannins, detected in 6 species, also play a key role in the antimicrobial and anti-inflammatory effects observed in the biological activities of medicinal Ni hyperaccumulators. These polyphenolic compounds interact with proteins and other biological macromolecules, inhibiting microbial growth and modulating inflammation (Singh & Kumar, 2020). Similarly, alkaloids in 5 species have long been studied for their analgesic and antimicrobial properties (Kurek, 2019), as confirmed by their biological activity.

On another note, the biological activities reported in the results further illustrate the potential of these Ni hyperaccumulator plants for medicinal use. The strong antimicrobial properties observed in 10 species of these plants are likely driven by flavonoids, tannins, and alkaloids, which are well-documented for their antimicrobial effects (Elvin-Lewis & Lewis, 1995; Wallace, 2004; Patel *et al*., 2012). The analgesic and anti-inflammatory activities identified in several species can also be attributed to the presence of these secondary metabolites, particularly flavonoids, tannins, and triterpenoids, which are known for their roles in pain relief and inflammation modulation (Liby *et al*., 2007; Ludwiczuk *et al*., 2017; Ullah *et al*., 2020; Singh & Kumar, 2020). Furthermore, rarer activities such as anticancer, anti-cholesterol, and antidiabetic properties are linked to specific secondary metabolites like coumarins and lignans. Coumarins, found in some of the plants in this study, have demonstrated anticancer and anti-inflammatory activities (Sarker & Nahar, 2017; Al-Warhi *et al*., 2020; Sharifi-Rad *et al*., 2021), while lignans have shown promising results in cancer prevention and hormone-related disorders (Sato & Matsui, 2012; Yoder *et al*., 2015; Xu *et al*., 2019). The diverse array of secondary metabolites found in Ni hyperaccumulators, including flavonoids, tannins, alkaloids, and triterpenoids, highlights their potential as sources of pharmaceutical compounds with diverse biological properties that could be valuable in the development of novel therapeutic agents, especially for conditions where existing treatments are insufficient.

Conservation strategies for nickel hyperaccumulator plants in Southeast Asia

Hyperaccumulator plants are ideal candidates for mine site restoration upon closure, rehabilitation of metal-polluted lands, and the basis for developing environmental technologies like phytoextraction to remove metals from soils. Coordinated efforts from scientists, industry, and government are essential to ensure the conservation of all metallophyte species for ecological preservation (Whiting *et al*., 2004). In Southeast Asia, both in-situ and ex-situ conservation strategies have been employed. In situ conservation focuses on safeguarding natural habitats. Approximately 8% of Sabah, Malaysia's land is designated as protected areas, which include ultramafic regions that harbor species like *Phyllanthus rufuschaneyi* (Bryan *et al*., 2013; Bouman *et al*., 2018). Habitat restoration is another key strategy involving the reintroduction of native hyperaccumulators to post-mining sites. This approach stabilizes soil and promotes ecosystem recovery (van der Ent *et al*., 2015).

Ex-situ conservation complements *in-situ* efforts by preserving plants outside their natural habitats. The 'Hyperaccumulator Botanical Garden' in Sabah, Malaysia, exemplifies this approach, cultivating 10–20 plants of each known Ni hyperaccumulator species in ultramafic soil (van der Ent *et al*., 2015). Micropropagation, a widely used *ex-situ* method, further supports conservation by enabling the asexual reproduction of plants in sterile, controlled environments using nutritive media (Fernando & Quimado, 2023). This technique has been applied to rare hyperaccumulators like *Hybanthus floribundus* (Violaceae), which was successfully propagated using a medium enriched with 5 μM N6-benzylaminopurine (BA) and 0.5 μM α-naphthaleneacetic acid (NAA) (Bidwell *et al*., 2001). Such methods ensure these species' genetic preservation and potential reintroduction into their native habitats.

In the Philippines, integrating conservation strategies is imperative to safeguard Ni hyperaccumulator plants, many of which remain understudied. This is particularly vital for species such as *R. niccolifera*, which are increasingly vulnerable to mining activities and habitat degradation. Beyond the ecological significance of Ni hyperaccumulators, these plants possess untapped pharmaco-medical potential, offering opportunities for sustainable applications. Aligning conservation efforts with scientific research ensures biodiversity preservation, supports ecological restoration, and drives advancements in pharmaceutical innovation.

CONCLUSION

Nickel hyperaccumulation has been a significant scientific discovery that has paved the way for phytoremediation in mining areas with high Ni concentrations. In addition to this application, Ni hyperaccumulators are recognized for their confirmed medicinal value from an ethnomedical perspective. They are supported by in vivo, in vitro, and related clinical studies on their phytochemistry, with antimicrobial properties being the most prominent biological activity. This insight can serve as baseline information for minimizing the impacts of Antimicrobial Resistance (AMR) by exploring antimicrobial medicinal plants as sustainable alternatives to synthetic drugs.

Notably, the results of the PCA highlight Ericales (0.98), Malpighiales (0.95), and Myrtales (0.92) as key orders strongly linked to medicinal properties and phytochemical diversity. However, many Ni hyperaccumulators still need to be evaluated for their medical efficacy and safety, though local communities use them to treat specific illnesses based on the bioactive compounds present in these plants. The phylogenetic approach is a valuable tool for identifying relationships between medicinal and non-medicinal plants within the same family, especially those containing similar phytochemicals for therapeutic applications. Further exploration of Ni hyperaccumulators in Southeast Asia's ultramafic vegetation, particularly those species with no reported medicinal uses, is highly recommended.

Such studies will uncover new opportunities for therapeutic applications, contribute to clinical research, and support conservation initiatives, ensuring the sustainable use of these unique plants.

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