

Upgrading Indonesian Local Ethnomedicinal Knowledge with Molecular Phylogenetics

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ABSTRACT

With at least 200 ethnic groups and 30.000 medicinal plants used in *Jamu* formulations, Indonesia is one of the largest natural drug dispensaries in the world. Ethnomedicine-directed bioprospecting has been used to accelerate drug discovery. Little is known about the coverage of ethnomedicinal studies in Indonesia. The quest to obtain drugs from plants also remains elusive. Nature-derived approved drugs worldwide have come mostly from drug-productive families that tend to be clustered in the phylogenetic tree, thus these families should be the basis of bioprospecting focus. We presented a review of ethnomedicinal research conducted across Indonesia and recommend strategic approaches to accelerate the translation of traditional knowledge into the clinic. We identified several plant species commonly used with similar or different purposes within different places, empirical pharmacological studies, regions that are understudied, and comparison with plants whose metabolites have been used for the development of approved medicine worldwide. Combination of ethnomedicinal knowledge with molecular phylogenetics, -omics, Bioactivity-guided bioprospecting, DNA barcoding, and Global Biodiversity Information Facility (GBIF) software will enable more efficient and environmentally friendly drug discovery process as well as commercial production. Altogether, this proposed method will be a game-changer in the exploration of the largely untapped chemical diversity of Indonesian flora.

Keywords: *Indonesia, ethnomedicine, molecular phylogenetics, Global Biodiversity Information Facility, DNA barcoding*

1. INTRODUCTION

Indonesia is the biggest archipelagic country in the world. Coupled with the tropical climate, Indonesia hosts various types of ecological niche for animals and plants, making Indonesia one of the biggest biodiversity vessels in the world [1-3]. The plants particularly have been used by the Indonesians for numerous purposes, one of them being a natural resource for natural drugs. Unlike Traditional Chinese Medicine (TCM) or Ayurveda from India, the ethnic groups in Indonesia have very few records about their knowledge on medicinal plants, instead, they passed them down to their descendants from time to time *viva voce*, as *Jamu* formulations [4]. These *Jamu* formulations have been used by the ethnic people as the cure for several types of disease [5,6] and inspirations for many synthetically synthesized drugs available around us now. Coinciding with our continuous needs for new effective drugs, Indonesia's plant biodiversity can still be leveraged for its potential as natural drug resources. Diverse ethnomedicinal research throughout Indonesia have been done from time to time, from the western part of

Indonesia like Batak Karo people from Sumatera island [7], Dayak Seberuang people in West Kalimantan [8], Kaili Inde people in Central Sulawesi [2], up to Eastern islands, namely Sasak people in West Nusa Tenggara [9] and Yali people in West Papua [10]. Among the ethnic groups across Indonesia, these people utilize the plants derived from the same families, making these families group of plants the "hot" repositories for new prospective natural drug discoveries. The similar utilization of plant types also enhances the safety, efficacy, and effectivity of these plants, as they produce the same after effect, which is to cure similar health problems. Although many plants are highly potential as the new natural drug resources, the need to assess their efficacy, effectivity, and safety must be ensured through numerous trials.

In this paper, we accentuate some potent plant candidates for drug developments that have undergone preliminary research, the understudied areas in Indonesia for novel exploration in natural drug discovery, also recommendations to accelerate the time-consuming natural drug bioprospecting.

II. METHODS

Information on ethnobotany and ethnomedicinal research were conjoined from at least 20 research publications across Indonesia. We compiled the potent plants based on their frequent use in many places throughout Indonesia with the same believed medicinal properties. Then, we checked and chose the plants based on the list of Clinical Based Herbal Medicine (phytopharmaca) and Science-Based Herbal Medicine (Obat Herbal Terstandar, OHT) from BPOM, also their empirical research data through various trials, such as clinically trialed and approved drugs.

III. RESULTS AND DISCUSSION

Ethnomedicinal Research Across Indonesia

Currently, there are approximately 200 ethnic groups dispersed within 13,000 islands in Indonesia [11,12]. These people adapt to their environment, employing the plants for diverse purposes. The practice of traditional healing exploiting the available surrounding plants has been done from ancient times. Indonesia alone employs not less than 30 thousand species of plants as traditional medication [13]. Most of the plants are also cultivated outside Indonesia but may differ in phytochemical

properties and concentration as they lived in unrelated nature, consequently affecting their therapeutic abilities.

Plants produce primary and secondary metabolites which are fundamentals for their lives. Secondary metabolites production can be affected by the external forces, with more unique properties than the primary metabolites. These secondary metabolites provide the bioactive properties for natural drugs, such as carbohydrates, lipids, proteins, and their derivatives, also other classes of substances including alkaloids, phenols, terpenoids and acetogenins. Each of these substances has its own bioactivity in various systems [14].

We chose these potential medicinal plant candidates in Table 1 based on their frequent use, either with similar or dissimilar therapeutic purposes. This basis helps us invalidating their safety and availability across Indonesia as they are used by diverse ethnic groups throughout Indonesia. Further, we also sorted them out with clinically approved medicinal plants (phytopharmaca) and science-based herbal medicines (OHT) to explore the other potential medicinal plants, besides the heavily commercialized ones. We found 11 species of plants from 10 families that are employed in at least 5 areas across Indonesia, either with similar or different purposes.

Table 1. Medicinal plants used in more than five places across Indonesia under various purposes

Medicinal plants used in more than 5 places across Indonesia				
Families	Species	Vernacular name	Places	Uses
Acanthaceae	<i>Graptophyllum pictum</i>	Daun Ungu, Daun Wungu (Java)	Jambi, Sumatera Halmahera island North Sumatera Lombok, NTB Central Sulawesi Sumbawa, NTB	Back pain, fever, headache, after birth, digestive problem, haemorrhoid and diuretic
Acoraceae	<i>Acorus calamus</i>	Jeringau, Dlingo (Java)	Serampas, Jambi, Sumatera Yogyakarta North Sumatera Central Sulawesi Tengger, Jawa Timur	Rheumatic, stomachache, tonic, fever, cough and diarrhea
Amaryllidaceae	<i>Allium sativum</i>	Bawang putih	Serampas, Jambi, Sumatera Yogyakarta North Sumatera Central Sulawesi Tengger, Jawa Timur	Headache, rheumatic, cholesterol, fever, toothache and ulcer
Arecaceae	<i>Areca catechu</i>	Pinang	Serampas, Jambi, Sumatera East Kalimantan Halmahera island North Sumatera Sumbawa, NTB Riau	Injury, malaria, toothache, skin burn, tonic, after birth and worm infection
	<i>Cocos nucifera</i>	Kelapa hijau (ijo)	Serampas, Jambi, Sumatera Yogyakarta Halmahera island North Sumatera Sumbawa, NTB	Back pain, nerve problem, tonic, food poisoning, fever and smallpox
Compositae	<i>Ageratum conyzoides</i>	Amis Kambing, Babandotan (Sundanese)	Serampas, Jambi, Sumatera Yogyakarta Halmahera island Lombok, NTB Central Sulawesi Riau	Injury, swelling, cough and cold
Euphorbiaceae	<i>Aleurites moluccanus</i>	Kemiri	Serampas, Jambi, Sumatera East Kalimantan North Sumatera Lombok, NTB Central Sulawesi Sumbawa, NTB Minahasa, North Sulawesi	Swelling, malaria, appetite, abscess, anti-bleeding, injury and cancer
Lamiaceae	<i>Vitex trifolia</i>	Legundi	Serampas, Jambi, Sumatera Yogyakarta North Sumatera Lombok, NTB Guguak Sarai, West Sumatera	Itchy, give birth and cold
Piperaceae	<i>Piper betle</i>	Sirih, Sirih Merah	Serampas, Jambi, Sumatera Yogyakarta Halmahera island North Sumatera Lombok, NTB Central Sulawesi Sumbawa, NTB Minahasa, North Sulawesi	Eye problem, <i>fluor albus</i> , cough, body odour, skin burn, fever, antiseptic, dental care, after birth and respiratory problem
Poaceae	<i>Saccharum officinarum</i>	Tebu	Serampas, Jambi, Sumatera Yogyakarta Halmahera island West Papua Guguak sarai, West Sumatera	Fever, kidney problem, eye problem, flu, stomachache and cough
Zingiberaceae	<i>Alpinia galanga</i>	Laos, Lengkuas	Serampas, Jambi, Sumatera Yogyakarta Halmahera island Jawa Tengah North Sumatera	Tinea versicolor, scabies, respiratory problem, diarrhea, cough and tonic

Many vernacular names available for *Graptophyllum pictum*, depending on their growth areas, for example, Daun wungu, pudding leaves in Jambi Sumatera [15], leleko in North Maluku (Halmahera Island) [5], and sate ati in Sumbawa, West Nusa Tenggara [16]. This plant can be utilized for health problems such as haemorrhoid, anti-inflammatory [17,18], antimicrobial for *Streptococcus* sp. [19], antioxidant [20], a hepatoprotective agent in rats [21], antidiabetic in mice [22] and antifertility [23]. Indonesian particularly use this plant to alleviate hemorrhoid problem by drinking their leaves' boiled water with a maximum of 7 leaves per day. Cautions for pregnant and lactating mothers, also children were stated [18]. Study about the chemical constituents in this species showed the presence of flavonoids, steroids, tannins, coumarins, saponins, anthraquinones, phenols, and carbohydrates [24]. The leaves of this plant have anthocyanins pigment besides chlorophyll, enabling them to have a purplish colour and desired as ornamentals [25].

Acorus calamus with their local name Jeringau or Dlingo (Javanese), are perennial herb with diverse distribution around the world. This herb has α - and β -asarone, phenylpropanoids, lignans, terpenoids, alkaloids, flavonoids, quinones, sterols, and many derivatives mostly in their rhizomes [26]. These phytochemical substances have the ability as antimicrobial and anticancer [27], in vitro tested antidiabetic [28], antioxidant [29], larvicidal [30], insecticides [31] also as antivirals for dengue [32]. This plant is one of the most used medicinal plants across Indonesia, with 104 ethnic groups known to utilize this species [33].

Bawang putih or garlic (*Allium sativum*) has been immensely used as spices by Indonesian people, in fact, this species also holds a vast number of medicinal properties. This species was found to have the ability to lower cholesterol in eggs [34], also as antidiabetic and lowering lipid in humans (clinically trialed) [35]. This plant contains sulphuric compounds, proteins and minerals, also allicin which has the ability as antimicrobials [14,36]. Other secondary metabolites, including flavonoids, phenols, terpenoids, and alkaloids are also present in this species [37]. Indonesian people consume this plant by directly chew on them or employ them as cooking material [18].

This species of Arecaceae member called (*Areca catechu*) pinang have various medicinal properties in Indonesia. Several studies have proven their therapeutic properties as antidiabetic agent [38], insecticide against *Coptotermes gestroi* [39], antilipidemic [40], antimicrobial against *C. albicans* [41], also anthelmintic in chicken (pre-clinical study) [42]. Besides rich in lipids, this plant also comprised of alkaloids, carbohydrates, glycosides, phenols, flavonoids, and saponins in hydro alcoholic extracts [41].

Cocos nucifera a member of the Arecaceae family has so many uses to cure diverse health problems around the world including Indonesia. Other than its medicinal properties, Kelapa Hijau or ijo are also interestingly applied as furniture, construction material, ornamentals, food, also fertilizers [43]. The chemical constituent in this species are known to be alkaloids, saponins, glycosides, quinones,

terpenoids, tannins, flavonoids, phenols, proteins [44], vitamin C, catechin, lauric acid, and L-arginine [45]. Kelapa, its vernacular name in Indonesia, exhibit the ability as antimalarial against *P. berghei* by in vivo testing in mice (pre-clinical study) [46], antioxidant activity [47], in vivo in pregnant women as preventive agent against morning sickness [48], skin problems reliever [18], also as anti-diarrhea tested in vivo using mice (pre-clinical study) [49].

Ageratum conyzoides are seasonal plants with the characteristic of fishy smells if wilted. They are also known as Babandotan (Sundanese) and Amis Kambing or fishy goat in English, although some places might have their own vernacular names. This plant has been extensively used for injuries in several places in Indonesia, including Jambi [15], Bogor [50], and North Maluku [5]. They can also be utilized as antibacterial against *Salmonella* sp. [51], rheumatoid arthritis in mice (pre-clinical) [52], antifungal [53], stress reducer in koi fishes [54], herbicide against weed *Cyperus rotundus* [55], anticancer in HeLa cells (in vitro) [56] also antidiabetic property in mice [57]. Phytochemical studies were validating the presence of saponins, alkaloids, steroids, flavonoids, phenols, tannins [58], also various essential oils in the class of Terpenes, Coumarins, and Chromeno [54]. Although this plant is also classified as weeds but the therapeutic ability exerted can outcompete and even benefit them in cultivation for medicinal purposes.

Kemiri or candlenut (*Aleurites moluccana*) is a species member of Euphorbiaceae family and has been used in Indonesia or internationally as food spice or condiment, dye material and medicine materials that mainly employing from their seeds [50]. In several places across Indonesia, ethnic groups utilize this plant for various purposes. This plant possesses the antimicrobial activity against *S. typhi*, *Vibrio cholera*, and *E. coli* [59], lowering cholesterol and lipid absorption [60], anti-inflammatory and antipyretic [61], also as an analgesic [62]. The plant constituent is dominated by the oil which consists of 50 compounds, i.e. hexanoic acid and 7,10-Hexadecadienoic acid, methyl ester [63], while the seed contains 9 compounds that are classified as acids [64]. The bark of this plant consists of alkaloid, flavonoid, polyphenol, quinone, tannin, and terpenoids [65].

Legundi is a member of Verbenaceae family with the scientifically approved name, *Vitex trifolia*. They are often used as decoration plants whilst exhibiting medicinal properties from their chemical constituents. Those medicinal properties include anti-inflammatory agent [66], hepatoprotective agent [67], larvicidal [68], healing property for skin injuries [69], also studied for their ability as an anticancer agent [70]. This species contains several chemical compounds including diterpenes, namely rotundifuran, dihydrosolidagenone, abietatriene 3 β -ol, also vitetrifolin A, B, C [71].

Piper betle or generally known as Sirih or Sirih Merah in Bahasa, are vine species of plant with uniquely heart-shaped leaf. The Indonesian people, especially elders like to chew on them, which in turn strengthens their teeth. They optimally live in humid areas with good soils, such

us Indonesian tropical forests [72]. Indonesians use this plant as one of their traditional healing materials for several purposes, which some of the uses, namely sore throat and antiseptic are consistent with Indonesian Ministry of Health's report in *Formularies of Indonesian Traditional Medicinal Plants* (FROTI). In the accepted formularies [18], Indonesians utilize this plant's healing properties by gargling the water used for boiling their leaves. The species' leaves contain numerous phytochemicals including alkaloid, phenol, flavonoid, tannins, saponins, terpenoids, steroids, also glycosides that each of them has therapeutic properties [73,74]. One of the constituent phenols are effectively inhibit bacterial infections by binding between the carboxyl group of phenols and proteins from bacteria. Up to date, many studies have been conducted invalidating their therapeutic properties such as antibacterial [73], antimalarial [75], antifungal [76], anti-inflammatory and antioxidant [77], also skin problems [78]. Other than its medicinal properties, this species is extensively used by many ethnic groups in Indonesia as their important rituals' material [79-81].

Saccharum officinarum or tebu (sugarcane) is a valuable commodity in Indonesia by encompassing many purposes in food, industry, medicine, even furniture from its residues (bagasse, designboom®). Indonesia alone produces this commodity up to 2.19 million tonnes and production area with around 420 thousand hectares in 2017 [82]. This species has many believed healing purposes by ethnic groups across Indonesia, as described in Table 1. They are comprised of phenols, flavonoids, phytosterols, and triterpenoids [83]. They act as an antioxidant [84] and anti-inflammatory agent [85], a hepatoprotective agent in rats [86], antimicrobial activity against *E. coli* and *P. aeruginosa* [87], immunomodulator in chicken [88], also an antifertility agent in rats [89].

Laos or lengkuas is a common cooking condiment employed by housewives throughout Indonesia. *Alpinia galanga* is a herbaceous plant which its rhizomes are widely used in medication, industries, and nutritious fields. They prefer warm places with high humidity for optimum growth and development [90]. They exhibit inhibiting activity against bacteria in fish preservation [91], antidiabetic property in rabbits [92], immunostimulant property [93], preventing stomachache [94], even inhibiting leishmanial parasites (in vitro) [95]. Components from this plant include β -bisabolene, (E)- β -farnesene, (E,E)-farnesyl acetate, (Z,E)- farnesol, β -caryophyllene from terpenoids class, as the major constituent. Other than that, numerous constituents numbering up to 60 compounds were observed in the study of *A. galanga*'s extracts [96].

The plants described before were chosen as they exhibit many medicinal properties either in vitro, pre-clinically, or clinically tested in humans. Some of the data were in concordance with the ethnic groups' beliefs of their medicinal properties. Most of the data collected were dominated by in vitro studies, while some therapeutic

beliefs haven't been scientifically tested. This is the gap that we scientists can fulfil by providing scientific data for further developments of these potential medicinal plants. The development of these plants may enhance the conservation of these plants and therapeutic alternatives.

Strategical Approaches to Accelerate the Bioprospecting of Novel Natural Drugs

Advancements in molecular technology will enable the researcher to integrate the use of phylogenetic, -omics approaches, DNA barcoding, and Global Biodiversity Information Facility (GBIF) to aid in the bioprospecting of novel natural drugs from medicinal plants. Studies that assessed the conserved orthologous gene of serine carboxypeptidase-like (SCPL) in the cross-species analysis were found in several plants were conducted. This SCPL gene plays a role in natural product construction which has the importance in plant defense [97,98]. The studies conducted using genomic and metabolomics disciplines to uncover the orthologous gene placement in cross-species' genome, may alleviate the number of 'hits' in ethnomedicinal studies.

Table 2. List of families and its genus representatives that are considered as hot nodes [99,100]

Hot nodes for bioactive constituent	
<i>Family</i>	<i>Genus</i>
Euphorbiaceae	<i>Aleurites</i> sp.
Fabaceae	<i>Acrocarpus</i> sp.
Asteraceae	<i>Myriactis</i> sp.
Malvaceae	<i>Abroma</i> sp.
Anacardiaceae	<i>Anacardium</i> sp.
Melastomataceae	<i>Medinilla</i> sp.

The molecular technology facilitates the study of underlying mechanisms on how these plants produce the desired substances, as well as identification of plants which have the most advantageous compounds' properties. The plants can produce the desired compounds because of evolution and adaptation to their surroundings. The production of these metabolites may support them in their survival against pathogens, climate change, or other substances that deter their life expectancy. As they evolved from the same basal organism, these groups of medicinal plants in one family or genus may have the same genes needed that code the desired substances [101, 102]. The assessment of rich bioactive-encompassed plants was done, resulting in various plants classified into family level groupings. Tens of families were obtained in different approaches [99,100]. These family groups are very potential for future bioprospecting as they were found to be bio actively rich plants. Examples of these families were given in Table 2. By that properties, natural drug discovery can be accelerated by a more focused approach, combined with DNA barcoding, these compelling technologies provide an accurate and precise screening of potent medicinal plants.

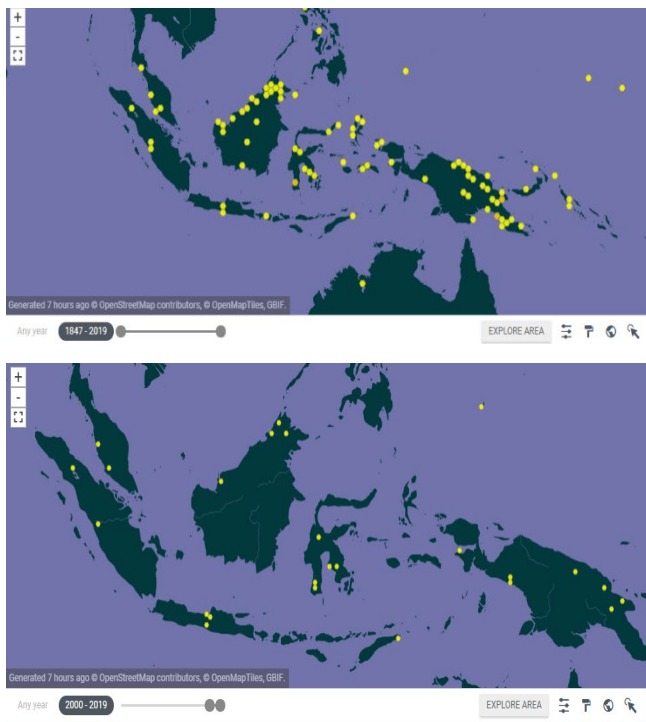


Figure 1. The distribution map of *Piper betle* (Sirih Merah) in Indonesia in the year 1847 (upper) and 2000 (below) based on GBIF.

Plants are prone to environmental cues that could impede their lives. Comparable to any other living things, plants can adapt to a certain environment and maintain their survival, either by modifying their physical structures or producing metabolites that hinder the predators or pathogens [103,104]. These metabolites that they produce can also be useful for humans as we might face the same kind of pathogens. Understanding the ecological repercussions to these plants will enable us to once again precisely and accurately predict the potent medicinal plants. Enhanced by the improving geographical information system (GIS) such as GBIF [105], the researcher can map the distribution and pinpoint the areas with a high occurrence of medicinal plants. An example of *Piper betle* distribution's mapping with GBIF in Figure 1 showed the decrease of occurrence of this species. The decreasing number of occurrences might be caused by little conservation or recording efforts. Although the implementation of this technology is still inadequate, but it possesses significant support in natural drug discovery through an ecological approach.

Based on the exploration of ethnomedicinal studies across Indonesia, the studies were mainly stressed in Java, Bali, Sumatera, Sulawesi, and Kalimantan islands, demonstrated by a vast amount of data of ethnomedicinal studies found. Although encompassed in the mentioned islands, some parts within the islands still have a scarce number of ethnomedicinal studies. Little data on the eastern part of Indonesian particularly in ethnomedicinal studies was observed. Combined with the fact of lifting the local people's quality of lives, places, ethnic groups, and cities of

West and East Nusa Tenggara also Papua provinces are potential for future studies. Even though there are several ethnomedicinal studies, but the low number of studies can be correlated with low number of areal coverage of studies from these provinces, conjoined with the fact of many dispersed ethnic groups within these provinces, enhancing their potential as new research area notably in ethnomedicinal studies. The approach based on combing the ethnic groups is also plausible to be done, in view of the fact that Indonesia is a repository for hundreds of ethnic groups.

IV. CONCLUSION

A total of 11 potential plants from 10 families are accentuated as potential medicinal plants to be explored in the future were presented. Three Provinces in Indonesia for further studies in ethnomedicinal areas were also described. These plants and areas are gaps to be fulfilled, which can be studied further for their pharmacology and potentials in many sectors such as research institutes and industries. Confronting a large amount of medicinal plant data, high-throughput screening methods such as -omics technologies, Bioactivity-guided prospecting and bioinformatics can provide a more efficient process in natural drug exploration and conservation strategies. A combination of these technologies will empower us in hastened bioprospecting of natural drugs from medicinal plants, particularly in the hot nodes within the phylogeny tree.

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