RESEARCH ARTICLE

# Phylogeny reveals non-random medicinal plant organ selection by local people in Benin

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[Correction added on 8 June 2021, after first online publication: 'organs' has been replaced with 'organ' in the article title.]

**Societal Impact Statement**

Humans rely on plants in their environment for food and medicine. Understanding how humans select plant species will help us anticipate what plant species will be valuable for society in the future. However, previous approaches to study the drivers of plant selection have been criticized. We explored medicinal plant selection using a refined methodology and corroborate that humans select plant species for medicine in a non-random way. Furthermore, we found that selection of specific plant organs across similar species is also non-random. Improved understanding of medicinal plant selection can help identify new medicinal plants and the particular organs of plant species that are most likely to contain bioactive compounds to help improve human health and well-being.

**Summary**

- Ethnobotany, the science of human–plant interactions, has for long focused on documenting the traditional knowledge that humans have developed and accumulated over centuries toward plant uses. However, how such knowledge is constructed remains poorly understood and some of the methodological approaches developed for this purpose have been criticized.

- Here, we combine negative binomial models and phylogenetic comparative methods to test whether selection of medicinal plant species and organs by local people are non-random using data from Benin, a country in West Africa with roughly 3,000 plant species.

- We found evidence for taxonomic and phylogenetic non-random selection of medicinal plants: some taxa are preferentially used for medicine. Our analysis uncovers that plant organs are also non-randomly selected for medicine. Beyond plant taxonomy, similar plant organs of closely related species tended to be used for similar treatments because these organs are likely to have similar secondary chemistry. Such non-random organ selection was more apparent for certain plant organs such as roots, bark, and leaves, which are predicted to be more vital for population fitness and species persistence.

- Collectively, our study suggests that the emerging non-random pattern of medicinal plant selection may be a consequence of heterogeneous within-plant

distribution of secondary chemistry across different organs proportionally to their importance to plant fitness as predicted by the optimal defense theory.

**KEYWORDS**
comparative phylogenetic methods, ethnobiology, medicinal flora, negative binomial model, non-random medicinal plant selection theory, optimal defense theory

## 1 | INTRODUCTION

In the face of the ongoing human-driven extinction crisis (Barnosky et al., 2011; Ceballos et al., 2015), understanding human–plant interactions is of practical importance as this can help regulate anthropogenic pressure on natural resources. However, in comparison with ecological studies, little effort has been devoted to uncovering what predisposes a given species to human selection for a particular use. Yet harvesting non-timber forest products (NTFPs) for medicinal or food purposes is widespread with significant implications not only for the livelihood of the people who depend on it (Belcher et al., 2005; Shackleton et al., 2005) but also for the ecological integrity of the systems that are harvested (Gaoue et al., 2013; Moegenburg & Levey, 2002; Silvertown, 2004; Ticktin, 2004). For example, wild plants and animals represent nearly USD 160 billion worth of products harvested and traded annually (Millennium Ecosystem Assessment, 2005) with the global sale of herbal medicine alone predicted to reach USD 130 billion by 2023 (Howes et al., 2020).

Human selection of medicinal plants has been considered a random behavior and their use based on a "placebo effect" (Adler & Hammett, 1973) or according to the doctrine of signature (Bennett, 2007). However, mounting evidence indicates that medicinal plant selection is non-random (Bennett & Husby, 2008; Gaoue et al., 2017; Muleba et al., 2021; Robles Arias et al., 2020; Staub et al., 2016). Such demonstration is important because more than 80% of local people rely on medicinal plants for primary healthcare particularly in low- and middle-income countries (Hamilton, 2004; Kaimowitz & Sheil, 2007), and establishing confidence in traditional healthcare is central to developing sustainable healthcare strategies, particularly in regions that lack other forms of medical cover (Salam & Quave, 2018; Vandebroek et al., 2011). In addition, recognizing the importance of local ecological knowledge and testing whether there is a biochemical basis for medicinal plant use is a critical step toward decolonizing science and global health (Büyüm et al., 2020; Vandebroek et al., 2020; Wheeler & Root-Bernstein, 2020).

Moerman (1979) was the first to demonstrate a taxonomic selectivity in plants used for medicinal purposes in North America. He used a linear regression of the form $y_i = \beta_1 + \beta_2 x_i + \varepsilon_i$ to show that the number of medicinal plant species ($y_i$) in a given family $i$ is a function (i.e., $\beta \neq 0$) of the total number of species in that family ($x_i$). The parameter $\varepsilon_i$ in this equation represents the sampling error. Moerman (1979) then analyzed the residuals of the linear regression model to group plant families into over- vs. under-utilized categories; thus, demonstrating the non-randomness of medicinal plant selection by local people. The use of "over/under-utilized" concept can *a priori* be misleading because it might suggest that these families are over-harvested. However, in the sense of Moerman et al., (1979), an over-utilized family is one that has more medicinal plant species than expected from the total number of plant species in that family. It does not indicate that these species are harvested beyond their maximum sustainable limits. A possible alternative could be "under/over-selected" medicinal plant families. However, we continued to use over-/under-utilized in this study to keep it consistent with previous tests of non-random hypothesis (e.g., Ford & Gaoue, 2017; Muleba et al., 2021; Robles Arias et al., 2020).

Moerman's approach inspired several other authors who provided additional support to the non-random plant selection (Amiguet et al., 2006; Bennett & Husby, 2008; Ford & Gaoue, 2017; Kapur et al., 1992; Muleba et al., 2021; Robles Arias et al., 2020). This approach advances our understanding of human–plant interactions. However, Moerman's approach has some limitations that can influence the classification of families in over- and under-utilized taxonomic groups. Specifically, using general linear models to explain the variation of a 'count data' (number of medicinal plants in a given family) ignores the requirement for normal residuals. To account for non-normal residuals, recent studies log-transformed the number of medicinal species per family before fitting a linear model (Ford & Gaoue, 2017) but models based on log-transformed count data (e.g., number medicinal species per family) tend to perform poorly (see O'Hara & Kotze, 2010). In the present study, we propose an alternative model suitable for modeling the relationship between family size and its richness in medicinal plants and compare the results to that obtained from the linear and log-transformed models to illustrate how model choice can influence the identification of medicinal plant families as over-/under-utilized.

In addition, we further the concept of non-random selection by suggesting that it is not only plant species that are selected on purpose, but within-plant selection or plant organ selection also follows non-random patterns. In addition, we suggest that a refined statistical approach (in comparison with Moerman's and most currently used analyses) coupled with a phylogenetic test, an emerging method in ethnobiological studies (Ernst et al., 2015; Lei et al., 2020; Saslis-Lagoudakis et al., 2011, 2014; Teixidor-Toneu et al., 2018; Yessoufou et al., 2015), would provide stronger evidence, for non-random plant use and a non-random selection of plants' organs by local people.

An over-utilization of some taxonomic groups for medicinal purpose (Ford & Gaoue, 2017; Moerman, 1979; Moerman & Estabrook, 2003) is an indication that these groups likely produce active bio-chemicals that are effective against certain diseases. This can be expected from the optimal defense theory (Albuquerque et al., 2012; Almeida et al., 2005; Coley et al., 2003; Lucena et al., 2012). This theory assumes that secondary compounds are heterogeneously distributed across different parts of a plant and predicts that plant organs that are most valuable for individual and population fitness would be more defended against diseases or herbivory and, therefore, have more secondary compounds that could be used as medicine by humans (McCall & Fordyce, 2010; Stamp, 2003). Therefore, one would expect plant organs that are important for plant fitness to be preferentially targeted by local people in their search for medicine. For closely related plant species, it is more likely that similar organs are targeted for medicine by local people and possibly for similar medicinal use. Surprisingly, the theoretical underpinnings of within-plant organs selection for medicinal purpose have received far less attention (but see Albuquerque et al., 2012) than the non-random selection of species or families (see Amiguet et al., 2006; Ford & Gaoue, 2017; Moerman, 1979).

In this study, we combined generalized linear models and phylogenetic analysis to understand how plant organs are likely to be selected in a non-random way by local people for medicine. We hypothesized that, beyond selecting for plant families with rich medicinal values, local people also select organs within a given plant species or family. We tested these hypotheses using the medicinal flora (507 species) of the entire country of Benin in West Africa. First, we assembled the first complete phylogeny of medicinal plant species in Benin. Second, we refined Moerman's approach to differentiating between over- and under-utilized medicinal plant families and demonstrate non-random medicinal plant and organ selection. Finally, we tested for phylogenetic signals in selection for medicinal plant organs across the flora.

## 2 | MATERIALS AND METHODS

### 2.1 | Data compilation

We studied the medicinal flora of Benin, a French-speaking country in West Africa covering an area of ~121,000 km$^2$ and harboring 12 million people. Benin is located between Nigeria in the east and Togo in the west. We compiled two types of data for our analysis: total plants list and medicinal plants list. We first digitalized the existing flora of Benin (Akoegninou et al., 2006) to retrieve species and family names and build the total plants list for Benin. We verified binomial name changes and family classification against APG IV using The World Flora Online (WFO, 2021). This flora includes 2802 angiosperms from 583 families. Second, to build the medicinal plants list for Benin, we obtained the most comprehensive compendium on Benin medicinal plants (Adjanohoun et al., 1989).

This compendium includes 507 medicinal plant species from 83 families and was commissioned by the French *Agence de Cooperation Culturelle et Technique* and developed by the best-known botanists of West Africa at that time. Two more recent medicinal plant studies focused on the southern region of Benin (Quiroz et al., 2014, 2016) but used market surveys. Although the list of medicinal plants reported in these new studies included new species (in comparison to Adjanohoun et al., 1989 list), it was not possible to judge if these were species from Benin or imported from neighboring countries to be sold in Benin markets. Particularly, species like *Prunus africana* or *Aframomum melegueta* which are not native to Benin and not included in Benin floristic database (Akoegninou et al., 2006) are found in the medicinal plant list compiled from the market survey (Quiroz et al., 2014, 2016). To avoid unnecessarily over-estimation of the number of medicinal plant species by including species sold in the markets and which may not be part of Benin native medicinal flora, we used the medicinal plant list in Adjanohoun et al., (1989). From these two (total and medicinal) plant lists, we build a dataset that includes for each plant family occurring in Benin, the total number of species, and number of medicinal species (see Dataset S1; Gaoue et al., 2021).

### 2.2 | Phylogeny of medicinal flora

We reconstructed a time-calibrated phylogeny for all 507 species used as medicinal in Benin. To this end, we compiled a matrix of 488 DNA sequences for the *matK* region, a marker used as DNA barcode. These sequences were retrieved for 488 species from GenBank/EBI and BOLD (www.boldsystem.org, accessed June 2017). For species for which DNA sequences are missing from these public repositories, we used DNA sequences from congeneric species that have their sequences on GenBank/EBI and BOLD. All GenBank/EBI and BOLD accession numbers for gene sequences are presented in Dataset S2 available at Dryad Digital Repository (Gaoue et al., 2021). Phylogeny reconstruction based on *matK* was performed using a Bayesian MCMC approach implemented in BEAST v. 1.4.8 (Drummond & Rambaut, 2007). We selected GTR +I + Γ as the best model of sequence evolution based on the Akaike information criterion (AIC) evaluated using MODELTEST v. 2.3 (Nylander, 2004). A speciation model following a Yule process was selected as the tree prior, with an uncorrelated lognormal model for rate variation among branches. We used the following secondary calibration points with a normal prior distribution based on (Magallón et al., 2015): Combretaceae SG (87.5 Ma), Leguminosae SG (55.3), Euphorbiaceae SG (37.2 Ma), Rhamnaceae SG (70.6 Ma), Rubiaceae SG (37.2 Ma), Malvaceae SG (55.8 Ma), and angiosperm crown (136 Ma). Monte Carlo Markov Chains (MCMC) were run for 100 million generations with trees sampled every 1000 generations. Convergence was checked using TRACER v. 1.5, and of the resulting 100 001 trees, we removed 15 000 as burn-in and combined the remaining 85 001 trees using TREEANNOTATOR v. 1.5.4 (Drummond & Rambaut, 2007).

## 2.3 | Non-random plant selection

We initially ran the general linear model of the number of medicinal species per family as a function of the total number of species per family (model 1) as commonly done in previous studies on this question (Amiguet et al., 2006; Moerman, 1979, 1996). As expected, we found strong departure from normal residuals and heteroscedasticity (Supporting information; Figures S1 and S2). We then log($x$+1) transformed the response and predictor variables (model 2) as done in a few studies (e.g., Ford & Gaoue, 2017) to address the normality and heteroscedasticity issues. Given that our response variable is a count data, such log-transformation which is commonly done can lead to suboptimal results (O'Hara & Kotze, 2010; Zeileis et al., 2007). To address this, we developed a generalized linear model with a Poisson error distribution:

$$y_i \sim Pois\left(\lambda_i\right) \tag{1a}$$

$$\log(\lambda_i) = \beta_1 + \beta_2 x_i + \varepsilon_i \tag{1b}$$

$$\varepsilon_i \sim N\left(0, \sigma^2\right), \tag{1c}$$

where $y_i$ is the true number of medicinal plant species per family $i$ which is modeled as a Poisson process with mean $\lambda_i$ that can be estimated given the number of plant species per family $x_i$. $\beta_1$ and $\beta_2$ are regression coefficients to estimate and $\varepsilon_i$ is the sampling error. However, due to data over-dispersion (variance of the response variable exceeding the mean), we finally developed a negative binomial model to account for over-dispersion (model 3):

$$y_i \sim NB\left(\lambda_i, \theta\right) \tag{2a}$$

$$\log(\lambda_i) = \beta_1 + \beta_2 x_i + \varepsilon_i \tag{2b}$$

$$\varepsilon_i \sim N\left(0, \sigma^2\right), \tag{2c}$$

where all the parameters are defined as in Equation (1a–c) except for the new parameter $\theta$ which represents the dispersion parameter of the negative binomial distribution (Nakagawa et al., 2017).

For each of these models, we identified over-utilized families as those with positive residuals indicating higher number of recorded medicinal species than would be expected from the fit of the model. A limited number of studies used a Bayesian approach modeling the proportion of total species that is medicinal as a binomial process (Weckerle et al., 2011, 2012), instead of the number of medicinal plant species per family (Poisson process) as we used in this study and in the original study of Moerman (1979). These two approaches are expected to yield similar results given that our analysis is based on a large countrywide sample size.

## 2.4 | Phylogenetic approach to test nonrandom plant organ selection

We tested for phylogenetic signal in organ selection for medicine. For this purpose, organs are coded as follows: 1, when an organ for a species is used to treat a given illness; and 0, when an organ is not used for any disease treatment (Dataset S3 in Dryad Digital Repository; Gaoue et al., 2021). To test for phylogenetic signal, we employed the $D$ statistic (Fritz & Purvis, 2010) specifically designed for binary variable (here, organ selection: selected vs. not selected) as implemented in the R library CAPER (function phylo.d; Orme et al., 2014). Fritz and Purvis (2010) designed the $D$ statistics to provide an estimate of phylogenetic signal specifically for binary variables. The observed $D$ values are interpreted as follows: $D = 1$ is indicative of a random distribution of organs selected for medicinal uses along the phylogeny (no phylogenetic signal); $D = 0$ indicates there is a phylogenetic signal in organ selection, following Brownian Motion (BM) model; $D < 0$ means there is stronger signal than expected while $D > 1$ signifies organ selection pattern is over-dispersed on the phylogeny (no signal). If the observed $D$ value is comprised between 0 and 1, we tested if the observed value departs significantly from 1 (random); a significant departure means organ selection is non-random along the phylogeny. Otherwise, the observed value is considered as random. The significance of $D$ value was tested comparing the observed $D$ values to the expected values while reshuffling the use pattern along the tips of the phylogeny. The signals in organ selections were illustrated graphically on the phylogeny using the R function *contMap* in the library *phytools* (Revell, 2012), allowing us to infer the probability of organ selection pattern in internal nodes. All analyses were conducted using R version 3.6.0 (R Core Team, 2019) and R scripts and data associated are available in Dryad Digital Repository (Datasets S1–S7 and Code S1; Gaoue et al., 2021).

## 3 | RESULTS

In the Benin flora, only 18% of total species richness is used for medicinal purpose. From a taxonomic perspective, depending on the analytical approach employed (negative binomial model, log-transformed model, and non-transformed model), 28–44% of the 83 medicinal plant families in Benin is more widely used for medicine than would be expected if medicinal plant selection by local people was random. This suggests that most medicinal families are under-utilized (Figure 1a). Using the best statistical model of all, that is, the negative binomial model (Figure 1b), the top 10 most over-utilized families include Combretaceae (+12.46), Malvaceae (+11.57), Apocynaceae (+10.56), Verbenaceae (+9.46), Moraceae (+8.88), Solanaceae (+8.60), Anacardiaceae (+8.30), Capparaceae (+7.16), Lamiaceae (+5.60), and Annonaceae (+4.80). However, the 10 top under-utilized are Leguminosae (−322351), Poaceae (−2607), Cyperaceae (−50), Rubiaceae (−42), Compositae (−29), Orchidaceae (−3.05), Euphorbiaceae (−2.06), Scrophulariaceae (−2.05), Asparagaceae (−1.55), and Pteridaceae (−1.46). It is important to note that this list of over-/under-utilized families changed when one

**FIGURE 1** Testing non-random medicinal plant selection to predict the number of medicinal plant species per family as a function of the total number of species per family. (a) We compare three models including a negative binomial regression (red), a log-transformed response variable (purple) and general linear models without transforming the response variable (blue); (b) inset showing the details for 20 by 100
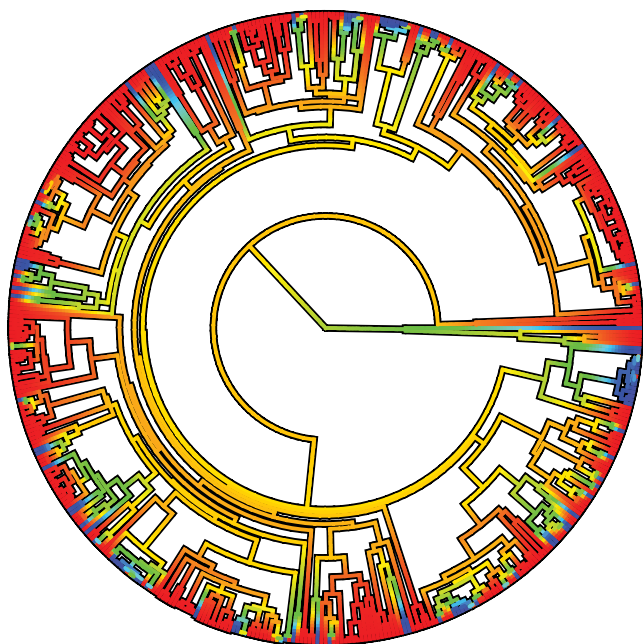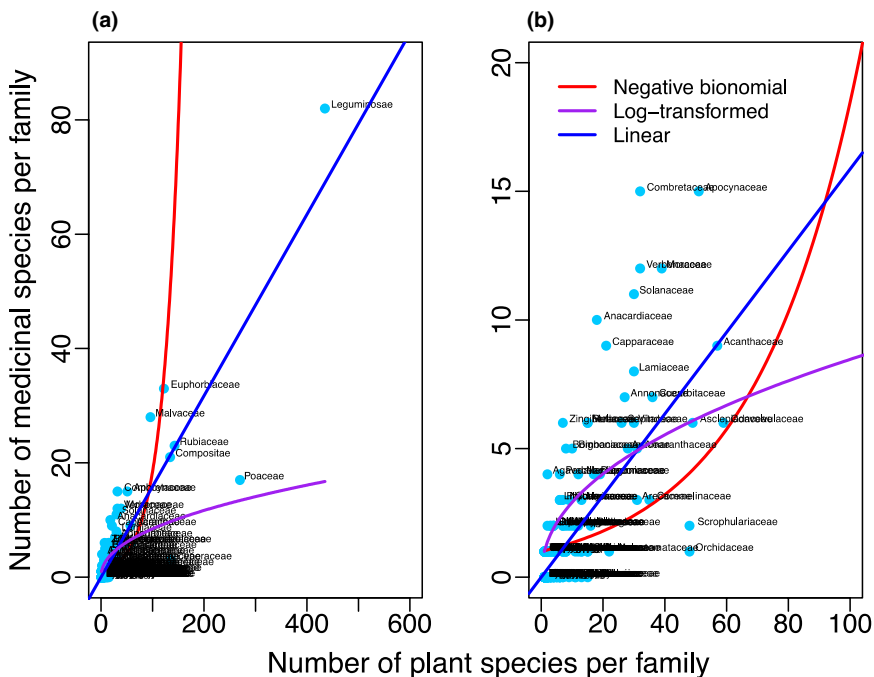


**FIGURE 2** Clustering patterns of plant species in over-utilized (blue) versus under-utilized families along the phylogeny. Significant phylogenetic signal for taxa over-utilization was tested using Fritz and Purvis' (2010) *D* statistic

considered the log-transformed model or the non-transformed model instead of the negative binomial model (Figure 1a). For example, the Leguminosae family which are under-utilized when the negative binomial model is used was wrongly classified as over-utilized when the non-transformed model is used.

Using a phylogenetic approach to further test the non-randomness of human–plant interactions, we found evidence of phylogenetic signal in over-utilized plants such that over-utilized species tend to cluster

on the phylogeny ($D = 0.64$; $P_{rand}$ <.001, Figure 2). This finding is consistently found, irrespective of how over- and under-utilized species are identified (i.e., irrespective of the models fitted), but the strength of the signal is highest with the negative binomial approach, which is the most appropriate of all models fitted, given the nature of the data (count data). Interestingly, we also found significant phylogenetic signal in the selection of plant organs used (Figure 3): root ($D = 0.50$, $P_{rand}$<.001), bark ($D = 0.30$, $P_{rand} < 0.001$), leave ($D = 0.53$, $P_{rand} < 0.001$), stems ($D = −0.15$; $P_{rand} < 0.001$), and fruits ($D = 0.65$; $P_{rand} = 0.006$).

This non-random plant organ selection is driven by different taxonomic clusters depending on the organs (Dataset S3; Gaoue et al., 2021). Specifically, the signal in the root selection for medicinal use is driven by the clusters of genera *Combretum*, *Protea*, *Vitex*, and *Sporobolus* (Figure 3a), whereas the signal in bark selection is driven by genera *Lannea*, *Pteleopsis*, *Afzelia*, *Erythrina*, and *Ficus* (Figure 3b). The selection of leaves is the most widespread across various clusters along the phylogeny; most of these clusters are shared with roots, suggesting that most of the time, when the roots of a plant are selected for medicinal use, leaves of the same plant are also likely to be selected. However, some clusters are unique to leaves such as *Opuntia*, *Calliandra*, *Cissampelos*, *Euphorbia*, *Physalis*, *Secamone*, *Terminalia*, etc. (Figure 3c). The selection of fruits is limited to only very few species dispersed in different isolated clades on the phylogeny; these species are found in the genera *Psidium*, *Mallotus*, *Tetrapleura*, *Citrus*, *Xylopia*, etc. (Figure 3d), whereas the selection of stems is mostly clustered within the genera *Opuntia* and *Cissus* (Figure 3e).

## 4 | DISCUSSION

In our study, the medicinal flora represents a low percentage (18%) of the total Benin flora, although this is within the range of

**(a)** Roots

**(b)** Barks

**(c)** Leaves

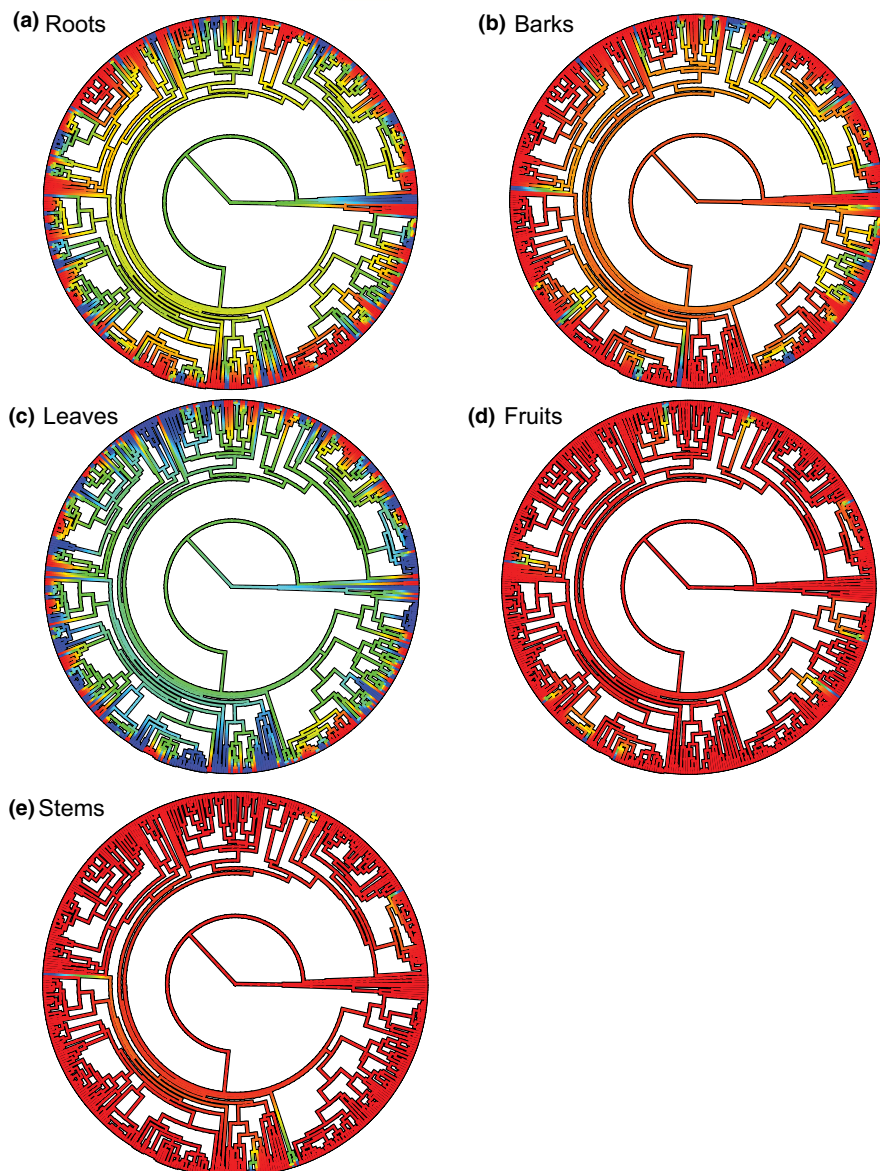**(d)** Fruits

**(e)** Stems



**FIGURE 3** Clustering patterns of plant organs used for medicinal purposes along the phylogeny. Plants whose (a) roots, (b) bark, (c) leaves, (d) fruits, or (e) stems are selected for medicinal use are clustered on the phylogeny (blue color). Significant phylogenetic signal for these organs was tested using Fritz and Purvis' (2010) *D* statistic

medicinal plant utilization rates elsewhere in Africa. Because people's knowledge of medicinal plants is shaped by the richness of their surrounding flora (Saslis-Lagoudakis et al., 2014), we would expect species-rich geographic regions to harbor more medicinal plants than not, as predicted by the theory of non-random medicinal plant selection (Bennett & Husby, 2008; Gaoue et al., 2017; Moerman, 1979; Moerman et al., 1999). However, we note that the identification of new medicinal species sold in Benin markets that are not native to Benin highlights that the total medicinal flora of the country is richer than presented in our study. That local people in Benin include non-native plant species in their ethnopharmacopoeia is not new (Ford & Gaoue, 2017; Hart et al., 2017; Palmer, 2004; Stepp, 2004; Stepp & Moerman, 2001), and this is consistent with the diversification hypothesis (Albuquerque, 2006; Alencar et al., 2010; Gaoue et al., 2017) that predicts the inclusion of alien species to enrich the locally available flora to treat an increasing number of diseases, some of which are new emerging disease. It is, therefore, in order that follow-up studies focus on the extent of such diversification and if this is

indeed driven by new emerging diseases (see Hart et al., 2017) or the shared influence of neighboring countries. We anticipate that over time there would be a homogenization of the medicinal flora of neighboring countries (Saslis-Lagoudakis et al., 2014), which can sustain progressive cross-cultural medicinal knowledge sharing, an important step in maintaining global sustainable medicinal systems.

Following this expectation, it is not a surprise that the proportion of medicinal flora in Benin contrasts quite well with that of the entire continent estimated at 25% of the 50 000 plant species in Africa (Iwu, 2014). These figures are more likely an underestimate of the total medicinal flora of the continent given that large part of its wilderness is under-explored (Sosef et al., 2017). However, the proportion of medicinal plants in Benin is higher than that of South Africa (13%, van Wyk et al., 1997; van Wyk & Gericke, 2000), a floristically mega-diverse country which is eight times more diverse than Benin (~24,000 species from 368 families; Germishuizen & Meyer, 2003). This adds to the mixed support reported for the availability hypothesis as a driving force of human–plant interactions

(Albuquerque, 2006; Gonçalves et al., 2016; Oliveira Trindade et al., 2015), and perhaps raises the need for a uniformity of what availability really means (Gaoue et al., 2017). Nonetheless, three reasons are likely to explain why Benin may have a proportionally greater medicinal flora than South Africa, although the latter is eight times more diverse than the former. First, it is possible that greater exploratory or screening efforts are still required (Hoveka et al., 2020) to reveal the full extent of the South Africa's medicinal flora. Second, previous studies show that human tends to know a limited number of plant species from their environment (Castiñeira Latorre et al., 2020; Hopkins & Stepp, 2012). Human cognitive restriction limits the number of medicinal plant species that one person can know. Cumulatively, such cognitive restrictions can limit the total number of medicinal plant species reported by local people in a given area independent of its size (Ferreira Júnior & Albuquerque, 2015). This may explain why even though South Africa has an eight-time larger flora, medicinal plant knowledge is not linearly related to the size of their flora. Third, and more importantly, it is very likely that the vast network of protected areas in South Africa (1527 National Parks, nature reserves, wilderness areas, mountain catchment areas, and World Heritage sites) precludes human interactions with a vast number of species (availability hypothesis), thus potentially leading to a misleading proportion of medicinal flora in South Africa. For example, the 9030 plant species of the Cape Floristic region, a protected area (biodiversity hotspot) with 68.7% endemic plants (Goldblatt & Manning, 2002) and the 1903 plant species of the Kruger National Park, which also harbors some endemic plants within its borders (Eckhardt et al., 2000; Venter, 1990), are not fully and all-time available for people's uses, given their status of protected areas. There is, therefore, a need to clarify how the concept of protected area limits traditional knowledge of medicinal plants to potentially blur the prediction of availability theory.

Despite the poor representation of medicinal flora in the total Benin flora, important patterns of human–plant interactions emerged. Specifically, we found that human–plant interactions in Benin are not a random behavior. Some plant families are over-utilized for medicine, but the proportion of over-utilized families is contingent upon the analytical approach used. Although the non-random plant selection hypothesis (Moerman, 1979) is widely tested and supported (e.g., Amiguet et al., 2006; Bennett & Husby, 2008; Ford & Gaoue, 2017; Kapur et al., 1992; Muleba et al., 2021; Phillips & Gentry, 1993), our analysis indicates a disparity in the volume of over-utilized species reported based on methods employed. Previous studies employed various methods to test the non-random hypothesis but the negative binomial, which is the best approach (given the "count data" nature of the variables used; O'Hara & Kotze, 2010; Zeileis et al., 2007), is hardly employed (Muleba et al., 2021; Robles Arias et al., 2020). Consequently, several taxa identified as over-utilized may actually be under-utilized and we call for a reassessment of the use patterns reported in those studies. Here, irrespective of the method used, we found evidence for non-random plant use such that 28% of Benin medicinal flora are medicinally over-utilized (negative binomial model). This indicates that most

families are under-utilized for medicine, thus raising key questions of whether some families are removed from medicinal utilization by protected areas, which are often specifically designed to protect important river watersheds, unique landscapes, or whether different geographic regions in the country may exhibit different use patterns due to heterogeneous human population density. These protected areas are also often less explored for ethnobotanical studies. This means that a family under-utilized at the country scale may be over-utilized in one region of the country, given that the environment shapes medicinal plant knowledge (Saslis-Lagoudakis et al., 2014).

At the country level, we identified the most over- and under-utilized families in Benin (negative binomial model). The families Combretaceae, Malvaceae, Apocynaceae, Verbenaceae, Moraceae, Solanaceae, Anacardiaceae, Capparaceae, Lamiaceae, and Annonaceae are over-utilized. Interestingly, four of these most over-utilized families (Combretaceae, Malvaceae, Apocynaceae, and Lamiaceae) are listed in the top drug-producing families (Zhu et al., 2011). The rest (except Capparaceae) is recently listed as high-priority families for future drug screening for various conditions: Verbenaceae for gynecological conditions; Moraceae for neurological problems; and Solanaceae, Anacardiaceae, and Lamiaceae for skin problems (Saslis-Lagoudakis et al., 2012). As such, it not a surprise that these families are over-utilized in Benin. Our study also reported some surprising findings. Families, such as Fabaceae, Poaceae, Rubiaceae, Compositae, and Euphorbiaceae, which are well known for their medicinal uses (Ford & Gaoue, 2017; Moerman, 1991; Moerman et al., 1999) are under-utilized in the Benin context, including the family Scrophulariaceae recently listed as high priority for drug screening (Pellicer et al., 2018; Saslis-Lagoudakis et al., 2011). This is likely due to the differences in the methodological approach used in various studies (here, we consistently report the findings based on our negative binomial model, a model not fitted in most studies). It is, however, not a surprise that Pteridaceae, Asparagaceae, Cyperaceae, and Orchidaceae are under-utilized because they contain limited amount of secondary chemistry (but see Simpson & Inglis, 2001).

In addition to this taxonomically non-random plant use, our analysis also pointed to phylogenetically non-randomness of plant selection as we found a strong phylogenetic signal in taxonomically over- versus under-utilized families (Figure 3). Similar evidence of a phylogenetic pattern in plant medicinal use is increasingly reported in recent studies (Ernst et al., 2015; Rønsted et al., 2012; Saslis-Lagoudakis et al., 2011; Yessoufou et al., 2015). Such evidence is not only a support to the non-random theory of human–plant interaction (Moerman, 1979), but it is also indicative of the power of phylogeny in guiding the bio-prospection of medicinal plants for drug discovery (Ernst et al., 2015; Lei et al., 2020; Saslis-Lagoudakis et al., 2011; Teixidor-Toneu et al., 2018).

Beyond the non-random taxonomic and phylogenetic pattern, our study also demonstrates that it is not just the plant that is non-randomly selected but also the organs used. Our finding of phylogenetic signal in plant organ selection suggests that similar organs are selected from closely related species for medicinal

use. This is an additional powerful support to the phylogeny as a tool to prioritize efforts in bio-screening for new drugs (Saslis-Lagoudakis et al., 2012). One explanation as to why similar organs from closely related species are medicinally used is predicted in the optimal defense theory (Pavia et al., 2002; Strauss et al., 2004), which indicates that most valuable organs for individual and population fitness would be more defended against diseases or herbivory and, consequently, would be rich in secondary compounds useful for humans as medicine (Stamp, 2003; Zangerl & Rutledge, 1996). Roots, bark, and leaves are central to plant's growth and survival particularly for long-lived species which dominate the medicinal plant list in our study region; e.g., population fitness is more sensitive to changes in survival (Adler et al., 2014). However, even though for short-lived species, reproductive investments are more important for population long-term fitness, it is rare that flowers and fruits are used specifically for medicine in our study region, unlike what is reported in other studies (e.g., Staub et al., 2016). This is most likely due to the fact that these reproductive organs are often short-lived thereby limiting their availability for specific development of medicinal knowledge. In addition, because flowers need to attract pollinators and mature ripen fruits need to attract frugivores and seed dispersers, high level of secondary compounds in these organs can make them less attractive to these mobile links and limit their primarily reproductive functions (but see exception for some Solanaceae, Sapindaceae, and Phytolaccaceae with toxic ripen fruits Cipollini & Levey, 1997).

In low- and middle-income countries, more than 80% of people rely on plant medicine as a primary source of healthcare (Hamilton, 2004; Kaimowitz & Sheil, 2007). Although the traditional knowledge accumulated over thousand years by local people are well documented in several parts of the world, it is only very recently that we start testing hypotheses and theories (Gaoue et al., 2017) to provide a better understand of human–plant interactions (Ford & Gaoue, 2017; Hart et al., 2017; Soldati et al., 2017). Our study falls within this recent trend, aiming to understand – rather than just documenting traditional knowledge – human–plant interactions. We found that plant or plant organ selections for medicinal uses are not a random behavior from both taxonomic and phylogenetic perspective. Instead, some taxa are over-utilized while others are under-utilized. Most of these taxa are well established as medicinal, and we provide here additional support to this. Other well-established medicinal taxa are not so in Benin (perhaps due to the different models fitted in different studies), pointing to how environment shapes medicinal knowledge (Saslis-Lagoudakis et al., 2014). More interestingly, we found that it is not just the plants but also the organs used that are not randomly selected, mirroring the prediction of the optimal defense theory.

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## CONFLICT OF INTERESTS

The authors declare no competing interests.

## AUTHOR CONTRIBUTIONS

OGG and KY conceived and designed the study. FV and LM collected the data; OGG, KY, and LM analyzed the data. OGG and KY wrote the paper and LM and FV provided revisions.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.