Phylogeny and bioprospecting: the diversity of medicinal plants used in cancer management

Thompson, J. B. ORCID: https://orcid.org/0000-0003-3784-5261 and Hawkins, J. A. ORCID: https://orcid.org/0000-0002-9048-8016 (2025) Phylogeny and bioprospecting: the diversity of medicinal plants used in cancer management. Plants, People, Planet, 7 (1). pp. 147-158. ISSN 2572-2611 doi: https://doi.org/10.1002/ppp3.10566 Available at https://centaur.reading.ac.uk/117917/

Received: 5 March 2024 | Revised: 5 July 2024 | Accepted: 31 July 2024

DOI: 10.1002/ppp3.10566

Plants People Planet PPF Open Access

RESEARCH ARTICLE

Phylogeny and bioprospecting: The diversity of medicinal plants used in cancer management

Jamie B. Thompson | Julie A. Hawkins

School of Biological Sciences, University of Reading, Reading, UK

Correspondence
Jamie B. Thompson, School of Biological Sciences, University of Reading, Reading, UK.
Email: j.b.thompson@reading.ac.uk

[Correction added on 30 August 2024, after first online publication: The placement of figures and tables has been improved in this version.]

Societal Impact Statement

As the second-leading cause of mortality worldwide, cancer is a major focus of drug discovery research. Traditional plant knowledge can guide the search for undiscovered compounds, but the efficacy of this approach for cancer, a highly complex disease affecting diverse tissues, is unknown. We investigated the patterns underlying plant selection for cancer treatment globally, finding certain lineages are repeatedly targeted. While this indicates therapeutic value, their relatedness with plants used for unrelated ethnobotanical uses suggests that plants are probably selected to treat cancer-associated symptoms, rather than addressing tumour growth. Careful re-examination and scoring of ethnobotanical reports may make the prediction of lineages for drug discovery more informative.

Summary

- Cancer is a highly diverse disease and as the second-leading cause of death worldwide is a focus of drug discovery research. Natural products have been shown to be a useful source of novel molecules for treating cancer. It is likely there are many plants with undiscovered molecules of therapeutic value, however identifying new leads from the vast diversity of plants is very challenging. Traditional knowledge might inform bioprospecting by predicting lineages of plants rich in therapeutically useful molecules.
- We characterise the phylogenetic diversity of plants used in traditional cancer management using a comprehensive genus-level phylogeny of angiosperms, and a list of 597 genera used globally to treat different cancers. We phylogenetically predict which lineages may have elevated potential for drug discovery and assess the quality of the prediction.
- We demonstrate the independent and repeated targeting of specific lineages of plants by different peoples in different parts of the world. However, the lineages we report here as rich in plants used in traditional cancer management coincide with those for other ethnobotanical applications and contain few plants with proven anti-cancer activity.

- That the same lineages are used to treat different cancers is suggestive of independent discovery of therapeutic value. However, it is likely that the traditional knowledge explored here is shaped by the selection of plants conferring milder effects for treating wider symptoms, such as tiredness or nausea, rather than for halting tumour growth. Accurate prediction of useful plant lineages for cancer management requires more nuanced information than is commonly provided in ethnobotanical records.

KEYWORDS

cancer, drug discovery, ethnobotany, medicinal plants, phylogenetics, plant diversity, prediction, traditional knowledge

1 | INTRODUCTION

Cancer is a diverse set of diseases affecting different organs, unified by abnormal growth and division of cells into tumours (Elia et al., 2015; Melo et al., 2013; Taylor et al., 2013). It is the second leading cause of mortality worldwide, responsible for a sixth of deaths (World Health Organisation, n.d.). Many modern anticancer pharmaceuticals have been derived from plants (Spjut & Perdue, 1976), including vinca alkaloids (Zhou & Rahmani, 1992), podophyllotoxin (Guerram et al., 2012) and taxanes (Shah et al., 2013). The contribution of plants to modern medicine is vast, with an estimated ~25% of pharmaceutical drugs, and as many as 60% of anti-tumour drugs derived from plants (Brower, 2008). While modern medicine relies on surgeries, radio- and chemo-therapy for cancer management, a large fraction of the world's population retains valuable traditional knowledge of plants used to manage cancer, which is well documented (Aumeeruddy & Mahomoodally, 2021). Correlative studies (Spjut & Perdue, 1976) and 'reverse-ethnopharmacology' (Leonti et al., 2017) have strongly linked traditional knowledge, but not specifically those related to cancer treatment, to known plant-derived biomedical cancer treatments, and those under clinical investigation. Plants in general, and those used in traditional medicine in particular, may represent an important source of novel molecules with therapeutic potential, but it is estimated that only 15% of plant species have been evaluated pharmacologically (De Luca et al., 2012; Verpoorte, 1998). The vast diversity of plants makes bioprospecting challenging, laborious and expensive (Firn, 2003), but we can use traditional knowledge to improve efficiency (Cox & Balick, 1994; Halse-Gramkow et al., 2016; Saslis-Lagoudakis et al., 2012). Characterising the phylogenetic diversity of plants used in local, folk medicine offers a method to expedite bioprospecting, by predicting lineages with elevated potential, so-called 'hot nodes' (Halse-Gramkow et al., 2016; Saslis-Lagoudakis et al., 2012). But this relies on the assumption that certain lineages used in traditional medicine are repeatedly targeted and that their properties are useful for modern cancer medicine.

A large fraction of the world's population in low- and middle-income countries still rely on traditional medicine to meet healthcare needs (Twarog & Kapoor, 2004) and plants are a large component of this, with an estimated 10,000–53,000 species of plants used traditionally (Schippmann et al, 2002; McChesney et al., 2007). Understanding human–plant relations has long been the focus of ethnobotanical research (Balick & Cox, 2020; Rahman et al., 2019), and is of growing practical importance. Traditional knowledge is being eroded through acculturation (Geck et al., 2016), language extinction (Cámara-Leret & Bascompte, 2021), and the availability of modern medicine. Similarly, plant diversity is being lost at an accelerated rate, largely due to human impacts (Antonelli et al., 2020; Nic Lughadha et al., 2020). It is vital not only to document traditional knowledge but also to understand patterns of medicinal plant selection (Gaoue et al., 2021; Souza et al., 2018; Teixidor-Toneu et al., 2018). Characterising the diversity of plants used in traditional medicine can not only highlight important plant lineages but may also improve confidence in traditional health systems because patterns are suggestive of a scientific basis. Furthermore, it reveals forces shaping cultural knowledge (Saslis-Lagoudakis et al., 2014; Teixidor-Toneu et al., 2018; Teixidor-Toneu, Kool, et al., 2021; Thompson et al., 2022).

It has long been demonstrated that several plant lineages are selected preferentially (Gras et al., 2021; Lei et al., 2020; Molander et al., 2012; Saslis-Lagoudakis et al., 2012), probably due to the discovery of lineage-specific phytochemistry. Phylogenetic comparative methods (PCMs) have been used to characterise patterns in the selection of medicinal plants in different contexts. Application of PCMs has revealed non-random lineage selection among distant cultures in specific genera (Saslis-Lagoudakis et al., 2011), entire ethnofloras (Lei et al., 2020; Saslis-Lagoudakis et al., 2011, 2012) and different aetiology systems (Lei et al., 2018). PCMs have revealed environmental and historical forces shaping knowledge (Saslis-Lagoudakis et al., 2014; Thompson et al., 2022), and non-random selection of plants targeting specific bodily systems including the nervous system and mind (Alrashedy & Molina, 2016; Halse-Gramkow et al., 2016; Rønsted et al., 2012). As well as providing evolutionary insights into ethnobotany, non-random selection strengthens support for the efficacy of traditional knowledge and has been argued to indirectly evidence bioactivity (Saslis-Lagoudakis et al., 2011). Support is strengthened when lineages are discovered independently by distant populations, instead of via cross-cultural transmission of knowledge (Teixidor-Toneu et al., 2018). However, many important diseases such as cancer

have been neglected, despite comprehensive documentation of global traditional knowledge (Aumeeruddy & Mahomoodally, 2021).

PCMs could provide insight into whether specific plant lineages are preferentially selected for the management of cancer, allowing prediction of lineages likely to harbour species with undiscovered utility, which has been demonstrated as a promising approach (Ernst et al., 2016; Halse-Gramkow et al., 2016; Pellicer et al., 2018; Saslis-Lagoudakis et al., 2011, 2012). However, the utility of this approach in traditional cancer management is unclear. Standardised medicinal use categories tend to be associated with bodily systems, and may not reflect underlying pharmacological action (Ernst et al., 2016; Staub et al., 2015). This can result in the selection of related lineages for use across disease classifications (Lei et al., 2020), making predictions of useful lineages misleading, depending on the level at which they are performed. The few phylogenetic investigations of medicinal plants in treating specific disease targets have focussed on single organ systems (Alrashedy & Molina, 2016; Halse-Gramkow et al., 2016; Rønsted et al., 2012) or ailments with similar pathologies (Molander et al., 2012). Plant drugs used for cancer management may encompass anti-tumour bioactivity, but also plant drugs without direct effects on a tumour. For example, some plants could provide a therapeutically important role in restorative nutrition, or have a supportive role in general health. Investigating phylogenetic clustering between plants used traditionally for cancer and plants with unrelated ethnobotanical applications might improve predictions of useful lineages. Plant-based drugs in clinical trials to treat cancer have been associated with plants used as poisons or as 'women's medicine' (Leonti et al., 2017). A subset of applications in women's medicine likely share an underlying property of cytotoxicity with poisons. However, other plant drugs used in women's medicine, such as some of the Fabaceae, rich in isoflavones, also referred to as phytoestrogens, would not be drawn from the same lineages as the poisons. These complexities may render the use of categories of traditional knowledge in bioprospecting for small molecules for directly treating tumours challenging. The efficacy of traditional knowledge in identifying and directly treating tumours is questionable, given the sophisticated diagnostic technology required for modern medicine to do so. It is likely that traditional knowledge systems address more obvious general health symptoms associated with cancer, such as weakness, lowered immunity and nausea.

Here, we assess phylogenetic patterns of global traditional cancer knowledge in angiosperms using a comprehensive genus-level phylogeny, and a dataset of 597 genera used to manage cancer. We reveal non-random selection of plants used against cancer, and for most organ-specific cancers, and assess the possibility of predicting undiscovered useful lineages. Extensive cross-predictivity in plants used across cancer types reduces our ability to predict useful lineages for specific organs, but the prediction is possible when considering cancer plants as a whole. However, further comparisons with plants undergoing clinical trials for cancer and for unrelated ethnobotanical uses suggest that many traditionally used plants confer mild effects that are likely to target symptoms associated with cancer. Our results caution that detailed investigations are needed when informing cancer bioprospecting with traditional knowledge.

2 | MATERIALS AND METHODS

2.1 | Data collection and processing

Genus-level data on flowering plants used in traditional cancer management were sourced from a recent and comprehensive systematic review, detailing 948 angiosperm species distributed in 153 families (Aumeeruddy & Mahomoodally, 2021). We recorded for each genus which cancer type it is used to manage, retaining only the top 10 most common cancer types, as reported by Aumeeruddy and Mahomoodally (2021), for the cancer-specific analyses (breast, cervix, colon, liver, lung, prostate, skin, stomach, throat and uterus), because the remaining 17 had too few plants for comparisons. No associations with cultures are provided, but country-level location data are described. We classified countries broadly into continents, which does not account for the fine-scale effects of geographical proximity, but provides a broad test of whether distant populations select plants from related lineages, despite compositional differences of local floras. We did not consider migrant communities, because it is unclear whether they retained knowledge from their homelands, or adapted to the new region (Medeiros et al., 2012).

Genera with various relevant ethnobotanical uses were sourced from the fourth edition of the comprehensive and authoritative Mabberley's plant book (Mabberley, 2017), compiled at genus level by Molina-Venegas et al. (2021). In this compilation, genera are sorted into 28 use categories, ranging from fuels and timber to food and medicine. We retained six categories that may be associated with plants selected for cancer management (food, food additives, medicines, invertebrate poisons, vertebrate poisons, and antifertility). Previous links have been made between cancer knowledge, poisons and antifertility drugs by Leonti et al. (2017). We additionally collected a list of genera in clinical trials for cancer (Zhu et al., 2011), compiled by Leonti et al. (2017).

2.2 | Phylogenetic analyses

2.2.1 | Testing for non-random selection of plants used in traditional cancer management

We used a large phylogeny of land plants sampling ~13,000 genera in all analyses (Hinchliff & Smith, 2014), pruning non-angiosperm genera to leave ~11,628. We performed analyses of phylogenetic structure using the R package phylocomr (Ooms et al., 2023), which implements community phylogenetic methods available in Phylocom (Webb et al., 2008). We tested whether plants used in traditional cancer management for any cancer type were phylogenetically clustered at deeper taxonomic levels, by calculating mean phylogenetic distance (MPD) with the command 'ph_comstruct'. 'Deeper taxonomic levels' here refers to phylogenetic clustering at deeper levels (e.g., tribal or sub-familial levels, given the genus-level sampling) (Lei et al., 2020). The observed MPD was compared with 9999 samples drawn randomly from across the phylogeny (null Model 2), and the number of comparisons for which the observed distance was smaller or larger than the null

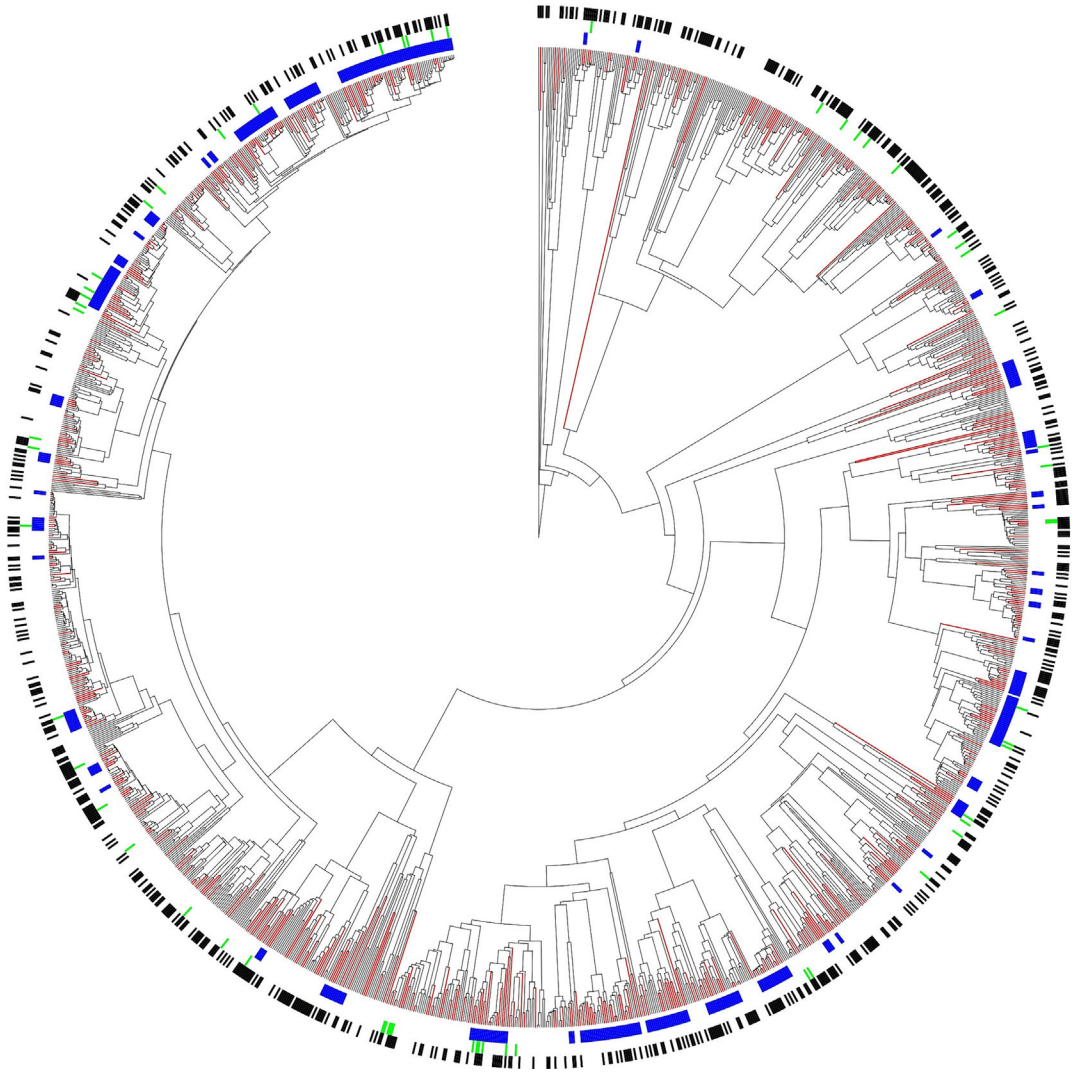

FIGURE 1 Phylogenetic distributions of genera used in traditional cancer management, genera producing biomedical drugs, clinical trial and preclinical trial drug candidates, and edible plants plotted alongside lineages with predicted utility for bioprospecting. Genera in traditional cancer management (red branches) are phylogenetically clustered within medicinal plants and across angiosperms generally. Hot node lineages for 'cancer genera' (blue bars) are shown, as are genera producing biomedical drugs, clinical trial and preclinical trial drug candidates (green bars), and genera including plants with traditional use as food or food additives (black bars) are indicated. Only 22 of 67 (~33%) genera producing biomedical drugs, clinical trial and preclinical trial drug candidates are found in hot nodes. A similar proportion of food plant genera are within hot nodes (275/1332; ~21%), suggesting different properties shape traditional cancer knowledge. For ease of interpretation, we pruned genera without known medicinal use as described by Mabberley (2017) from the angiosperm tree in this figure, but analyses use all angiosperm genera unless specified otherwise.

samples was calculated. From this, two-tailed *p*-values and net relatedness index (NRI) were calculated. A positive NRI indicates clustering while a negative indicates overdispersion, and significance is reached at >1.96 and <−1.96, respectively (at an alpha threshold of $p < .05$ in a two-tailed p test). We also tested whether plants used in traditional cancer management were a phylogenetically clustered subset of those used generally across traditional medicine. To do this, we estimated NRI on the same phylogeny, but with genera without medicinal or cancer use pruned, using the list of medicinal genera in Molina-Venegas et al. (2021) and cancer genera in (Aumeeruddy & Mahomoodally, 2021). We tested for non-random selection by populations across the world despite geographic distance, cultural evolution and floristic differences among continents. This involved comparing NRI estimates of pairwise comparisons of plants used on each continent (estimated with the command 'ph_comdist') with the complementary metric nearest taxon index (NTI). NTI is calculated in the same manner as NTI using the command 'ph_comdistnt', but the metric mean nearest taxon distance (MNTD) is used instead of MPD. NTI brings insight into whether plants are selected from related lineages on a shallower taxonomic level (Lei et al., 2020). We assessed whether genera used in the management of the 10 best-reported individual cancer types are clustered at deeper taxonomic levels, with NRI.

2.2.2 | Testing for relationships between plants used for different cancer types, and with other ethnobotanical applications

We ran pairwise comparisons to understand the relatedness of genera selected for different cancer types, by calculating NRI between samples used for the top 10 most frequently reported cancer types, using the command 'ph_comdist'. We ran pairwise NRI comparisons between plants used against cancer and plants used for the six previously described unrelated ethnobotanical uses (antifertility, food and food additives, vertebrate and invertebrate poisons and medicines).

2.2.3 | Prediction and description of lineages with elevated bioprospecting potential

We predicted hot nodes for cancer with the command 'nodesig' in Phylocom (Webb et al., 2008). This analysis identified lineages that were significantly overrepresented by genera used in traditional cancer management. To ensure we had effectively reduced the search for useful plants, we considered only hot nodes, which contained up to 100 tips, following Halse-Gramkow et al. (2016).

2.2.4 | Data visualisation

We visualised the phylogenetic distributions of traditionally used plants with the Interactive Tree of Life v5 (Letunic & Bork, 2021). To visualise the two examples of predicted useful lineages, we used the R package ggtree (Yu et al., 2016). Heatmaps showing relatedness among different plant uses were produced with the R package ggplot2 (Wickham, 2011).

3 | RESULTS

3.1 | Non-random selection of lineages used in traditional cancer management

Plants used in traditional cancer management overall (all types of cancer) are selected from related higher taxonomic lineages within angiosperms (NRI 9.09, $p < .05$), and the subset of ~1600 angiosperm genera with medicinal use reported by Mabberley (2017) (NRI 3.32, $p < .05$) (Figure 1). 'Related higher taxonomic lineages' here refers to phylogenetic clustering at deeper levels (e.g., tribal or sub-familial levels, given the genus-level sampling) (Lei et al., 2020). Similarly,

TABLE 1 Phylogenetic clustering of genera used in traditional cancer management. Net relatedness index (NRI) is presented and significance indicated with an asterisk. Clustering is assessed for genera with use across all cancer types within angiosperms generally, and within medicinal genera as described by Mabberley (2017). Clustering of genera used for specific cancer types is assessed within angiosperms.

Target	Number of genera	Tree	NRI	Pattern
All cancers	597	Angiosperm genera (~11,600)	9.09*	Clustered
All cancers	597	Angiosperm genera pruned to include only genera used medicinally (~1600)	3.32*	Clustered
Breast	165	Angiosperm genera	5.30*	Clustered
Cervical	19	Angiosperm genera	2.5*	Clustered
Colorectal	46	Angiosperm genera	1.68	No pattern
Liver	26	Angiosperm genera	0.30	No pattern
Lung	59	Angiosperm genera	4.33*	Clustered
Prostate	56	Angiosperm genera	2.92*	Clustered
Skin	137	Angiosperm genera	4.56*	Clustered
Stomach	72	Angiosperm genera	1.88	No pattern
Throat	44	Angiosperm genera	2.15*	Clustered
Uterus	36	Angiosperm genera	2.09*	Clustered

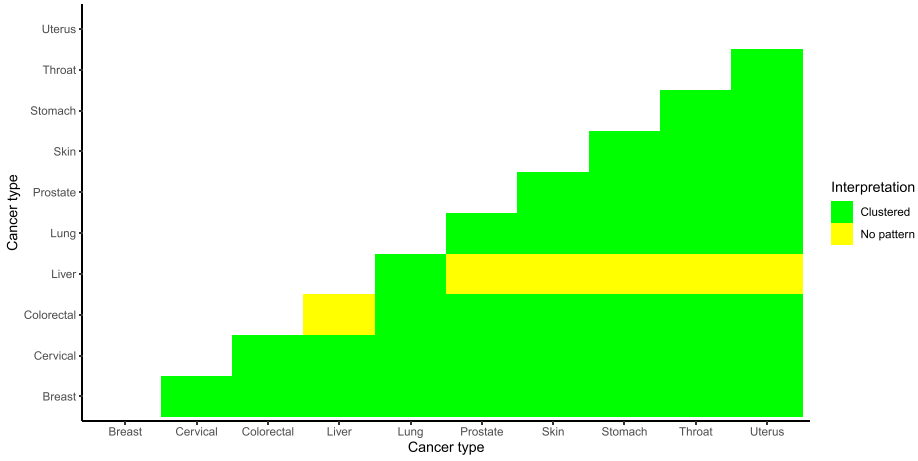

FIGURE 2 High cross-predictivity of lineages used for different cancer types reduces ability to predict organ-specific useful lineages. Genera used for specific cancers were selected from related lineages, except that only three of nine pairwise cross-comparisons that included genera used for liver cancer were significant. Significance is defined here as a net relatedness index (NRI) is greater than 1.96.

plants used to manage specific cancers are significantly selected from related deep lineages (NRI > 1.96, $p < .05$), with the exception of plants used to manage colorectal, liver and stomach cancers, which show neither clustering nor overdispersion (NRI > −1.96 and <1.96, $p > .05$) (Table 1).

3.2 | Related lineages are targeted for use across most cancer types

Pairwise comparisons of clustering between genera used for cancers of different organs reveal high levels of cross-predictivity (Figure 2). Generally, certain lineages are repeatedly targeted for the management of different cancers (NRI > 1.96, $p < .05$), with the exception of most comparisons with liver cancers, for which no pattern is found.

TABLE 2 Plants used in traditional cancer management are drawn from deep lineages related to those of plants used for food and food additives, medicines across all therapeutic applications and poisons. They are not clustered with lineages with antifertility uses. Net relatedness index (NRI) is presented and significance indicated with an asterisk.

Ethnobotanical use	Number of genera	NRI	Interpretation
Antifertility	56	1.01	No pattern
Food	1182	4.29*	Clustered
Food additives	330	4.58*	Clustered
Invertebrate poisons	181	5.37*	Clustered
Medicines	1392	9.58*	Clustered
Vertebrate poisons	128	3.69*	Clustered

3.3 | Cross-predictivity between use in cancer and other ethnobotanical uses

Plants used traditionally for cancer management are selected from related deep lineages to those used for food, food additives, medicines, vertebrate poisons and invertebrate poisons (NRI > 1.96, $p < .05$), but not for antifertility uses (NRI > −1.96 and <1.96, $p > .05$) (Table 2).

3.4 | Independent discovery of useful lineages across continents, despite floristic variation

With the exception of Oceania, populations across continents select closely related deep lineages for cancer treatment (NRI > 1.96) (Figure 3a), but these are unrelated at shallower taxonomic depths (Figure 3b). 'Shallower taxonomic depths' here refers to clustering closer to tip level (Lei et al., 2020). At the shallower phylogenetic depth, several cross-continental comparisons are overdispersed (Africa and Asia, Africa and Europe, Asia and South America, Europe and North America) (NTI < −1.96), and no pattern is found for the remaining comparisons.

3.5 | Predicting lineages with elevated bioprospecting potential

After confirming a high level of cross-predictivity in plants used for specific cancers, we predicted lineages with elevated utility against cancer generally. We identified 1548 genera as having an elevated likelihood of harbouring useful activity (~13.31% of angiosperm genera sampled in the phylogeny), including 260 of

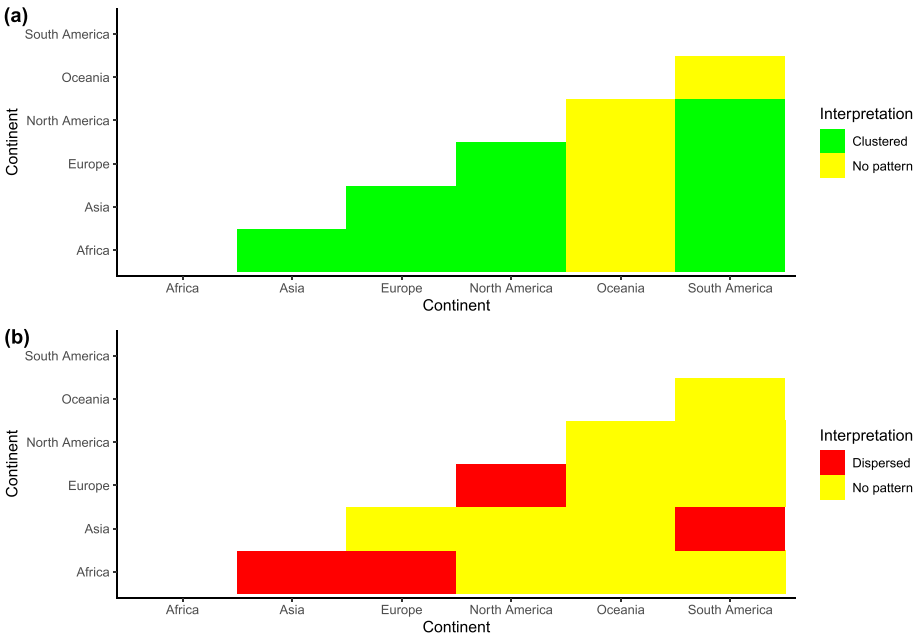

FIGURE 3 Distant populations select genera for traditional cancer management from related lineages (a), despite unrelatedness or even overdispersion at shallower taxonomic levels (b). Angiosperm floras differ across the globe, meaning that the same plants will not necessarily be available for selection.

the 597 cancer genera. These are distributed across 51 families, and the five families with the highest representation are Fabaceae (226 genera), Lamiaceae (208), Asteraceae (133), Apocynaceae (99) and Cucurbitaceae (99). Two examples are plotted in Figure 4, demonstrating the predictive approach, and the full list of genera is given in Dataset S1. Of the 67 genera under investigation for cancer treatment in clinical trials, only 22 are found in the hot nodes (*Aglaia*, *Brucea*, *Catharanthus*, *Cicer*, *Dysoxylum*, *Indigofera*, *Larrea*, *Lavandula*, *Lens*, *Matricaria*, *Medicago*, *Mentha*, *Monarda*, *Ochrosia*, *Perilla*, *Pisum*, *Salvia*, *Silybum*, *Tabebuia*, *Tabernaemontana*, *Trifolium* and *Vicia*).

4 | DISCUSSION

4.1 | Plants used for cancer treatments are non-randomly selected

Our study shows that plants used traditionally for cancer management are phylogenetically clustered within angiosperms and within all medicinal plants (Figure 1, Table 1). The repeated targeting of certain lineages for therapeutic properties may indicate the discovery of bioactive phytochemistry or useful pathways that are evolutionarily conserved (Halse-Gramkow et al., 2016; Saslis-Lagoudakis et al., 2011, 2012). When cross-cultural transmission of knowledge is low, similarities in medicinal knowledge can be interpreted as arising via independent discovery (Hawkins & Teixidor-Toneu, 2017; Saslis-Lagoudakis et al., 2011, 2012; Teixidor-Toneu et al., 2018; Thompson et al., 2022). Independent discovery supports the view that plant medicines are efficacious (Bletter, 2007; Saslis-Lagoudakis et al., 2011, 2012). Bletter (2007) writes at length about independent discovery and efficacy and cites the anti-diabetic properties of *Azadirachta indica* as an example of cross-cultural independent discovery of efficacy. We found that plants used for cancer management are unrelated at lower taxonomic levels across continents, and so unlike Bletter (2007), we do not highlight shared species. Rather, we find that plants used for cancer treatments are selected from related deep lineages, with the exception of Oceania (Figure 3). Relatedness at higher but not shallow evolutionary levels suggests the selection of different plants from related, independently discovered lineages. Oceania holds knowledge not shared with other regions (Lloyd Jones & Sadgrove, 2015), likely explained by the evolutionary distinctiveness of the Oceanic flora (Carta et al., 2021).

4.2 | There are preferred plant lineages for treating most types of cancer

Considering plants used to treat each different cancer in turn, we showed that seven out of 10 cancers were treated with plants that had a phylogenetic structure (Table 1). The lack of phylogenetic clustering of plants used against colorectal, liver and stomach cancers might be explained by cancer-specific properties. For instance, liver cancers are very complex pathologically, with multiple causes including toxin exposure, genetics and hepatitis infections (Fan et al., 2013). Similarly, stomach cancers have complex causes including tobacco and infection by *Helicobacter pylori* (Balakrishnan et al., 2017). Variation in causes and symptoms may lead to the

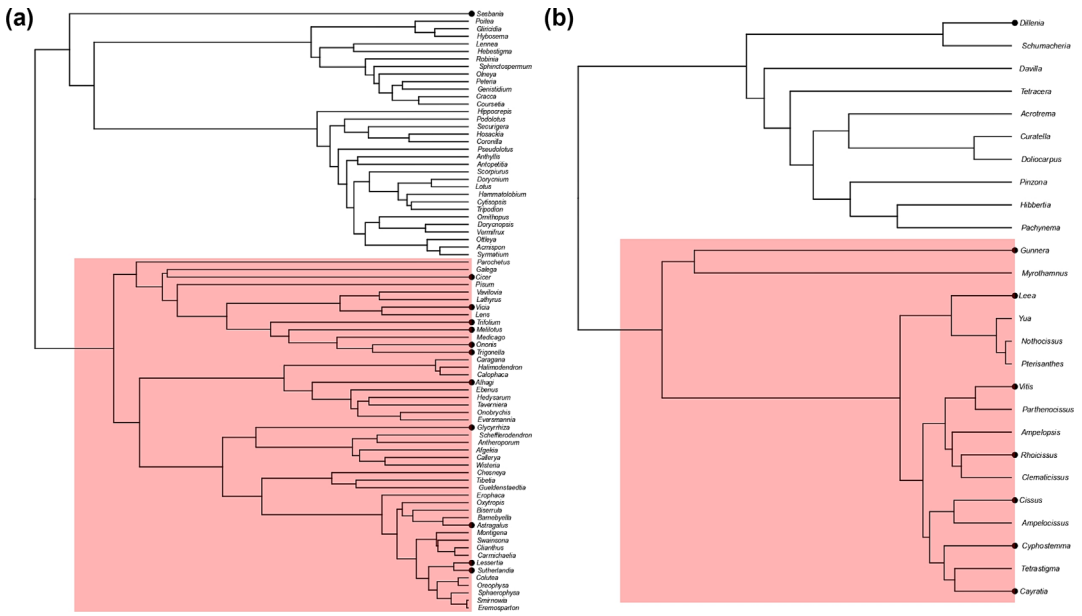

FIGURE 4 Two examples of angiosperm lineages with elevated value for cancer bioprospecting, predicted by phylogenetic distributions of traditional knowledge. The predictive approach is demonstrated in two randomly selected cases. Genera with traditional use for managing cancer are denoted by a black circle at the tips, and the lineage with predicted elevated value is highlighted in red. Based on phylogenetic predictions alone, the red lineages should be prioritised in bioprospecting.

selection of unrelated plants due to different lineage-specific properties. Several plants used against liver cancers are also used traditionally for hepatitis, with useful phytochemicals including oleanolic acid found in *Salvia*, and curcumin found in Zingiberaceae genera (Anand & Lal, 2016). Similarly, there is an overlap between plants used traditionally against stomach cancers and for *H. pylori* infection, including *Alchornea*, *Allium*, *Calotropis* and *Terminalia* (Safavi et al., 2014). The presence of symptoms associated with comorbid infections may drive plant selection from unrelated lineages with different properties. A possible repercussion of the lack of clustering is that traditional knowledge is ineffective in identifying useful plant drugs for these organ-specific cancers.

4.3 | Related lineages of plants are used across cancer types

Whether selection is for cancers of specific organs, or the same plant drugs are used for different types of cancers, may be important for informing bioprospecting. A previous study showed the same plant lineages were used for the same specific therapeutic applications by people in different parts of the world, and this was interpreted as an independent discovery of specific bioactivity (Saslis-Lagoudakis et al., 2012). It was based on these and similar observations that Saslis-Lagoudakis et al. (2012) suggested that phylogenetic approaches to identify independent discovery of specific therapeutic applications would be meaningful. However, recent research has cautioned against over-interpreting predictive patterns identified for specific therapeutic applications, because of high levels of cross-predictivity between therapeutic applications (Lei et al., 2020). We found that with the exception of plants used to treat liver cancers, related lineages are used to treat all cancers. Shared use of lineages across cancer types may be because therapeutic uses depend on general cytotoxic phytochemistry, targeting cellular processes underlying all cancer types perhaps by inducing cell death via inhibition of mitosis, DNA and ribosomal synthesis (Habli et al., 2017). Some of the most important plant-derived compounds used in clinical cancer medicine target multiple cancer types, including paclitaxel from the Pacific yew tree (*Taxus brevifolia*) (Priyadarshini & Keerthi, 2012), and vinblastine and vincristine, derived from the Madagascar periwinkle (*Catharanthus roseus*) (Mishra & Verma, 2017).

4.4 | Plants used against cancer include plants selected for cytotoxic properties

Leonti et al. (2017) used reverse ethnopharmacology to identify the traditional uses of plant drugs where proven value to biomedicine had been demonstrated. They found a statistically significant association between biomedical drugs with anticancer applications and traditional uses for cancer therapy, but also a significant association between biomedical applications in cancer therapy and a subset of traditional women's medicine, a broad category that includes dysmenorrhoea and uses as emmenagogues, contraceptives and abortifacients (Leonti et al., 2017). Supposing that a shared underlying property of cytotoxicity explained abortifacient properties, Leonti's findings supported the observations of Spjut and Perdue (1976) that plants with uses as poisons were more likely to show cytotoxic effects. Later, a phylogenetic study of the frequency of use of plants in ethnomedicine found that plants outside of the lineages that were frequently used appeared to have greater potential as leads in cancer medicine, as evidenced by the frequency of clinical trials for plants outside of hot nodes (Souza et al., 2018). Plants that lay outside of hot nodes, but were nevertheless used in ethnomedicine, were plants of infrequent use and strong effect and this too was attributed to the relationship between toxicity and potential as leads for the development of anti-cancer drugs (Souza et al., 2018).

The distinction between plants used frequently for mild effects, and plants used infrequently for strong effects led us to explore whether there was cross-predictivity between uses for different therapeutic categories. We found clustering between plants used traditionally for vertebrate and invertebrate poisons and those used for cancer, suggesting that at least some of our hot nodes harbour cytotoxic phytochemicals that may be useful for cancer therapeutics. Support for the efficacy of traditional knowledge in identifying lineages with medicinal potential is strengthened by patterns of clustering between these two categories of use. Indeed, ethnobotanical data collected by Mabberley (2017) and categorised by Molina-Venegas et al. (2021) reported 292 genera, including poisonous species; of these genera, 95 were among the 597 plant genera, including species used for cancer treatment. However, while Leonti et al. (2017) might suggest clustering between plants used for anti-fertility and cancer treatment, we find no such relationship here. This might be because the anti-fertility category we use, from Molina-Venegas et al. (2021), includes drugs that are abortifacients but also plant drugs that are contraceptives or otherwise used for fertility control. It therefore likely encompasses plant drugs of very different effects, although some would have cytotoxic properties.

4.5 | Plants used in cancer management include plants selected for properties unrelated to tumour growth

The fact that the plants used in cancer treatment are significantly clustered with food plants indicates that properties unrelated to cytotoxicity are commonly selected (Figure 1, Table 1). This result is not unexpected, because 328 of the 597 genera with plants used for cancer treatments in our study are among the 1332 genera with uses as foods or food additives, as described by Molina-Venegas et al. (2021). The boundary between foods and medicines can be blurred, and the perception of medicines as food and foods as medicines is well-documented (Etkin, 2008; Etkin & Ross, 1982, 1991; Johns, 1990, Moerman, 1994; Teixidor-Toneu, Elgadi, et al., 2021). The abundance

of useful phytomolecules in food, such as antioxidants and nutrients, means edible plants are commonly used as medicines (Cisneros-Zevallos, 2021). As many as one third of plants used medicinally may be cultivated primarily as foods (Alqethami et al., 2017). Treatment of symptoms associated with cancer is likely treated with plants of mild effect, including food plants. Sufferers of cancer are commonly fatigued, with weakened immune systems. Food plants may be used medicinally to relieve these and other side effects. Many edible plant-derived antioxidants and anti-inflammatory compounds have been studied in modern biomedicine. These include curcumin in turmeric, lycopene in tomatoes and resveratrol in grapes (Russo et al., 2010).

4.6 | Can we identify lineages with elevated bioprospecting potential?

Lineages with higher proportions of medicinally-used taxa than expected by chance have been referred to as hot nodes, and several studies report hot nodes for medicinal plants overall or for specific therapeutic applications (Cantwell-Jones et al., 2022; Ernst et al., 2016; Halse-Gramkow et al., 2016; Milliken et al., 2021; Saslis-Lagoudakis et al., 2011, 2012). We estimated hot nodes despite finding cross-prediction between specific cancer types, reasoning that these might be lineages with broad-spectrum anticancer properties. We identified ~13.31% of angiosperm genera in 51 families with likely-elevated utility against cancer according to the hot nodes approach (Dataset S1). While this appears to offer a framework to improve future bioprospecting efforts, it is notable that just 22 of 67 genera (32.83%) with phytochemicals of known biomedical utility, or investigated in clinical trials for use against cancer are present in the hot nodes. If, as previously discussed, therapeutic uses of plants in the treatment of cancer conflate gentle plants to support well-being and aggressive plants that might have anti-tumour activity, we might find a higher proportion of the plants in clinical trials in hot nodes that are significantly richer in plants used to treat cancer but which are not also food plants. The hot nodes reported here include 275 of 1332 food-plant genera (20.66%); we caution that these plants may be a mixture of those selected for general symptoms and those with truly anti-tumour properties.

Our data suggest that plants used in traditional cancer management are diverse pharmacologically, and may encompass plants of mild effect for strengthening the patient, and plants with cytotoxic effects that might reduce cancer growth. The data that we used came from a secondary source that recorded the type of cancer, but not the specific therapeutic goal of the plant drug intervention. Whether plants were used, for example, to manage nausea, was not recorded. Ethnobotanical data as reported in most publications may be insufficiently nuanced to distinguish lineages likely to harbour anti-tumour phytochemicals or have milder effects. Previous research into the utility of disease classification in traditional medicine has suggested that bodily categorisation performs poorly, and information on underlying biological responses is necessary (Ernst et al., 2016). Our findings similarly caution against interpreting classifications of therapeutic uses as pharmacologically meaningful. Where the goal of a bioprospecting endeavour is to identify potential anti-tumour compounds for cancer treatment, we recommend an ethnobotanically-informed phylogenetic exploration of plant poisons rather than one based on therapeutic application to treat cancer.

As well as more nuanced use of therapeutic classification, there is also scope for improved future analyses to account for intrageneric and interspecific/within plant variation. Our analysis identifies lineages and uses generic-level data. Species-level analyses are not uncommon in phylogenetic investigations of plant use (Cantwell-Jones et al., 2022; Leonti et al., 2024; Teixidor-Toneu, Kool, et al., 2021). This is important because intrageneric variation can be significant, for example, the herb tarragon (*Artemisia dracunculus*) is an edible condiment, but leaves of *Artemisia annua* contain cytotoxic compounds used for malaria treatment, which are under investigation for cancer treatment (Ferreira et al., 2010). Species-level data are not always readily available, however (e.g., Molina-Venegas et al., 2021). To date, analyses have not attempted to account for known variations in plant parts used. In many ethnobotanically-important species, different plant parts express different compounds, for example, *Taxus* leaves contain the highly toxic paclitaxel, but the arillus is edible. Ethnobotanical data at the level of plant part are needed ultimately, in order to understand and make use of the taxon lists that are the output of phylogenetic investigations.

AUTHOR CONTRIBUTIONS

Jamie B. Thompson and Julie A. Hawkins planned and designed the research. Jamie B. Thompson collected and analysed data. Jamie B. Thompson wrote the first draft of the manuscript. Jamie B. Thompson and Julie A. Hawkins edited the manuscript.

ACKNOWLEDGEMENTS

We acknowledge Cam Webb for advice with Phylocom.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

All analysed data are publicly available, with details provided in Section 2. Analyses were performed with statistical packages in R, and code is available upon request.

ORCID

Jamie B. Thompson https://orcid.org/0000-0003-3784-5261
Julie A. Hawkins https://orcid.org/0000-0002-9048-8016

REFERENCES

Alqethami, A., Hawkins, J. A., & Teixidor-Toneu, I. (2017). Medicinal plants used by women in Mecca: Urban, Muslim and gendered knowledge. *Journal of Ethnobiology and Ethnomedicine*, *13*, 62. https://doi.org/10.1186/s13002-017-0193-4

Alrashedy, N. A., & Molina, J. (2016). The ethnobotany of psychoactive plant use: A phylogenetic perspective. *PeerJ*, *4*, e2546. https://doi.org/10.7717/peerj.2546

Anand, K., & Lal, U. R. (2016). Hepatitis and medicinal plants: An overview. *Journal of Pharmacognosy and Phytochemistry*, *5*, 408–415.

Antonelli, A., Smith, R. J., Fry, C., Simmonds, M. S., Kersey, P. J., Pritchard, H. W., & Qi, Y. D. (2020). State of the world's plants and fungi 2020. Available at: https://www.kew.org/read-and-watch/state-of-the-world-plants-fungi-2020 [Accessed April 13, 2023].

Aumeeruddy, M. Z., & Mahomoodally, M. F. (2021). Global documentation of traditionally used medicinal plants in cancer management: A systematic review. *South African Journal of Botany*, *138*, 424–494. https://doi.org/10.1016/j.sajb.2021.01.006

Balakrishnan, M., George, R., Sharma, A., & Graham, D. Y. (2017). Changing trends in stomach cancer throughout the world. *Current Gastroenterology Reports*, *19*, 36. https://doi.org/10.1007/s11894-017-0575-8

Balick, M. J., & Cox, P. A. (2020). *Plants, people, and culture: The science of ethnobotany*. Garland Science. https://doi.org/10.1201/9781003049074

Bletter, N. (2007). A quantitative synthesis of the medicinal ethnobotany of the Malinké of Mali and the asháninka of Peru, with a new theoretical framework. *Journal of Ethnobiology and Ethnomedicine*, *3*, 36. https://doi.org/10.1186/1746-4269-3-36

Brower, V. (2008). Back to nature: Extinction of medicinal plants threatens drug discovery. *JNCI Journal of the National Cancer Institute*, *100*, 838–839. https://doi.org/10.1093/jnci/djn199

Cámara-Leret, R., & Bascompte, J. (2021). Language extinction triggers the loss of unique medicinal knowledge. https://doi.org/10.1101/2020.12.03.407593

Cantwell-Jones, A., Ball, J., Collar, D., Diazgranados, M., Douglas, R., Forest, F., Hawkins, J., Howes, M. J. R., Ulian, T., Vaitla, B., & Pironon, S. (2022). Global plant diversity as a reservoir of micronutrients for humanity. *Nature Plants*, *8*, 225–232. https://doi.org/10.1038/s41477-022-01100-6

Carta, A., Peruzzi, L., & Ramírez-Barahona, S. (2021). A global phylogenetic regionalisation of vascular plants reveals a deep split between Gondwanan and Laurasian Biotas. https://doi.org/10.1101/2021.04.09.439199

Cisneros-Zevallos, L. (2021). The power of plants: How fruit and vegetables work as source of nutraceuticals and supplements. *International Journal of Food Sciences and Nutrition*, *72*, 660–664. https://doi.org/10.1080/09637486.2020.1852194

Cox, P. A., & Balick, M. J. (1994). The ethnobotanical approach to drug discovery. *Scientific American*, *270*, 82–87. https://doi.org/10.1038/scientificamerican0694-82

De Luca, V., Salim, V., Atsumi, S. M., & Yu, F. (2012). Mining the biodiversity of plants: A revolution in the making. *Science*, *336*, 1658–1661. https://doi.org/10.1126/science.1217410

Elia, I., Schmieder, R., Christen, S., & Fendt, S.-M. (2015). Organ-specific cancer metabolism and its potential for therapy. *Metabolic Control*, *233*, 321-353. https://doi.org/10.1007/164_2015_10

Ernst, M., Saslis-Lagoudakis, C. H., Grace, O. M., Nilsson, N., Simonsen, H. T., Horn, J. W., & Rønsted, N. (2016). Evolutionary prediction of medicinal properties in the genus *Euphorbia* L. *Scientific Reports*, *6*, 30531. https://doi.org/10.1038/srep30531

Etkin, N. L. (2008). *Edible medicines: An ethnopharmacology of food*. University of Arizona Press.

Etkin, N. L., & Ross, P. J. (1982). Food as medicine and medicine as food: An adaptive framework for the interpretation of plant utilization among the Hausa of northern Nigeria. *Social Science & Medicine*, *16*, 1559–1573. https://doi.org/10.1016/0277-9536(82)90167-8

Etkin, N. L., & Ross, P. J. (1991). Should we set a place for diet in ethnopharmacology? *Journal of Ethnopharmacology*, *32*, 25–36. https://doi.org/10.1016/0378-8741(91)90100-r

Fan, J.-H., Wang, J.-B., Jiang, Y., Xiang, W., Liang, H., Wei, W.-Q., Qiao, Y. L., & Boffetta, P. (2013). Attributable causes of liver cancer mortality and incidence in China. *Asian Pacific Journal of Cancer Prevention*, *14*, 7251–7256. https://doi.org/10.7314/apjcp.2013.14.12.7251

Ferreira, J. F., Luthria, D. L., Sasaki, T., & Heyerick, A. (2010). Flavonoids from *Artemisia annua* L. as antioxidants and their potential synergism with artemisinin against malaria and cancer. *Molecules*, *15*(5), 3135–3170. https://doi.org/10.3390/molecules15053135

Firn, R. D. (2003). Bioprospecting—Why is it so unrewarding? *Biodiversity and Conservation*, *12*, 207–216. https://doi.org/10.1023/a:1021928209813

Gaoue, O. G., Yessoufou, K., Mankga, L., & Vodouhe, F. (2021). Phylogeny reveals non-random medicinal plant organ selection by local people in Benin. *Plants, People, Planet*, *3*, 710–720. https://doi.org/10.1002/ppp3.10202

Geck, M. S., Reyes García, A. J., Casu, L., & Leonti, M. (2016). Acculturation and ethnomedicine: A regional comparison of medicinal plant knowledge among the Zoque of southern Mexico. *Journal of Ethnopharmacology*, *187*, 146–159. https://doi.org/10.1016/j.jep.2016.04.036

Gras, A., Hidalgo, O., D'Ambrosio, U., Parada, M., Garnatje, T., & Vallès, J. (2021). The role of botanical families in medicinal ethnobotany: A phylogenetic perspective. *Plants*, *10*, 163. https://doi.org/10.3390/plants10010163

Guerram, M., Jiang, Z.-Z., & Zhang, L.-Y. (2012). Podophyllotoxin, a medicinal agent of plant origin: Past, present and future. *Chinese Journal of Natural Medicines*, *10*, 161–169. https://doi.org/10.3724/sp.j.1009.2012.00161

Habli, Z., Toumieh, G., Fatfat, M., Rahal, O., & Gali-Muhtasib, H. (2017). Emerging cytotoxic alkaloids in the battle against cancer: Overview of molecular mechanisms. *Molecules*, *22*, 250. https://doi.org/10.3390/molecules22020250

Halse-Gramkow, M., Ernst, M., Rønsted, N., Dunn, R. R., & Saslis-Lagoudakis, C. H. (2016). Using evolutionary tools to search for novel psychoactive plants. *Plant Genetic Resources*, *14*, 246–255. https://doi.org/10.1017/s1479262116000344

Hawkins, J. A., & Teixidor-Toneu, I. (2017). Defining 'ethnobotanical convergence'. *Trends in Plant Science*, *22*, 639–640. https://doi.org/10.1016/j.tplants.2017.06.002

Hinchliff, C. E., & Smith, S. A. (2014). Some limitations of public sequence data for phylogenetic inference (in plants). *PLoS ONE*, *9*, e98986. https://doi.org/10.1371/journal.pone.0098986

Johns, T. (1990). *With bitter herbs they shall eat it: Chemical ecology and the origins of human diet and medicine*. University of Arizona Press. https://doi.org/10.2307/j.ctv1qwwj2q

Lei, D., Al Jabri, T., Teixidor-Toneu, I., Saslis-Lagoudakis, C. H., Ghazanfar, S. A., & Hawkins, J. A. (2020). Comparative analysis of four medicinal floras: Phylogenetic methods to identify cross-cultural patterns. *Plants, People, Planet*, *2*, 614–626. https://doi.org/10.1002/ppp3.10131

Lei, D., Wu, J., Leon, C., Huang, L., & Hawkins, J. A. (2018). Medicinal plants of Chinese pharmacopoeia and daodi: Insights from phylogeny and biogeography. *Chinese Herbal Medicines*, *10*, 269–278. https://doi.org/10.1016/j.chmed.2018.06.004

Leonti, M., Baker, J., Staub, P., Casu, L., & Hawkins, J. (2024). Taste shaped the use of botanical drugs. *eLife*, *12*, RP90070.

Leonti, M., Stafford, G. I., Cero, M. D., Cabras, S., Castellanos, M. E., Casu, L., & Weckerle, C. S. (2017). Reverse ethnopharmacology and drug discovery. *Journal of Ethnopharmacology*, *198*, 417–431. https://doi.org/10.1016/j.jep.2016.12.044

Letunic, I., & Bork, P. (2021). Interactive tree of life (itol) V5: An online tool for phylogenetic tree display and annotation. *Nucleic Acids Research*, *49*, W293–W296. https://doi.org/10.1093/nar/gkab301

Lloyd Jones, G., & Sadgrove, N. J. (2015). Ethnopharmacology in Australia and Oceania. *Ethnopharmacology*, 365–378. https://doi.org/10.1002/9781118930717.ch31

Mabberley, D. J. (2017). *Mabberley's plant-book: A portable dictionary of plants, their classification and uses*. Cambridge University Press. https://doi.org/10.1017/9781316335581

McChesney, J. D., Venkataraman, S. K., & Henri, J. T. (2007). Plant natural products: Back to the future or into extinction? *Phytochemistry*, *68*, 2015–2022. https://doi.org/10.1016/j.phytochem.2007.04.032

Medeiros, P. M., Soldati, G. T., Alencar, N. L., Vandebroek, I., Pieroni, A., Hanazaki, N., et al. (2012). The use of medicinal plants by migrant people: Adaptation, maintenance, and replacement. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 807452. https://doi.org/10.1155/2012/807452

Melo, F. D., Vermeulen, L., Fessler, E., & Medema, J. P. (2013). Cancer heterogeneity—A multifaceted view. *EMBO Reports*, *14*, 686–695. https://doi.org/10.1038/embor.2013.92

Milliken, W., Walker, B. E., Howes, M.-J. R., Forest, F., & Nic Lughadha, E. (2021). Plants used traditionally as antimalarials in Latin America: Mining the tree of life for potential new medicines. *Journal of Ethnopharmacology*, *279*, 114221. https://doi.org/10.1016/j.jep.2021.114221

Mishra, J. N., & Verma, N. K. (2017). A brief study on *Catharanthus Roseus*: A review. *International Journal of Research in Pharmacy and Pharmaceutical Sciences*, *2*, 20–23.

Moerman, D. L. (1994). *Eating on the wild side: The pharmacologic, ecologic, and social implications of using noncultigens*. University of Arizona Press.

Molander, M., Saslis-Lagoudakis, C. H., Jäger, A. K., & Rønsted, N. (2012). Cross-cultural comparison of medicinal floras used against snakebites. *Journal of Ethnopharmacology*, *139*, 863–872. https://doi.org/10.1016/j.jep.2011.12.032

Molina-Venegas, R., Rodríguez, M. Á., Pardo-de-Santayana, M., Ronquillo, C., & Mabberley, D. J. (2021). Maximum levels of global phylogenetic diversity efficiently capture plant services for humankind. *Nature Ecology & Evolution*, *5*, 583–588. https://doi.org/10.1038/s41559-021-01414-2

Nic Lughadha, E., Bachman, S. P., Leão, T. C., Forest, F., Halley, J. M., Moat, J., et al. (2020). Extinction risk and threats to plants and fungi. *Plants, People, Planet*, *2*, 389–408. https://doi.org/10.1002/ppp3.10146

Ooms, J., Chamberlain, S., & Sanchez Reyes, L. (2023). phylocomr: Interface to 'Phylocom'. https://docs.ropensci.org/phylocomr/, https://github.com/ropensci/phylocomr

Pellicer, J., Saslis-Lagoudakis, C. H., Carrió, E., Ernst, M., Garnatje, T., Grace, O. M., Gras, A., Mumbrú, M., Vallès, J., Vitales, D., & Rønsted, N. (2018). A phylogenetic road map to antimalarial *Artemisia* species. *Journal of Ethnopharmacology*, *225*, 1–9. https://doi.org/10.1016/j.jep.2018.06.030

Priyadarshini, K., & Keerthi, A. U. (2012). Paclitaxel against cancer: A short review. *Medicinal Chemistry*, *02*, 139-141. https://doi.org/10.4172/2161-0444.1000130

Rahman, I. U., Afzal, A., Iqbal, Z., Ijaz, F., Ali, N., Shah, M., Ullah, S., & Bussmann, R. W. (2019). Historical perspectives of ethnobotany. *Clinics in Dermatology*, *37*, 382–388. https://doi.org/10.1016/j.clindermatol.2018.03.018

Rønsted, N., Symonds, M. R., Birkholm, T., Christensen, S., Meerow, A. W., Molander, M., et al. (2012). Can phylogeny predict chemical diversity and potential medicinal activity of plants? A case study of Amaryllidaceae. *BMC Evolutionary Biology*, *12*, 182. https://doi.org/10.1186/1471-2148-12-182

Russo, M., Spagnuolo, C., Tedesco, I., & Russo, G. L. (2010). Phytochemicals in cancer prevention and therapy: Truth or dare? *Toxins*, *2*, 517–551. https://doi.org/10.3390/toxins2040517

Safavi, M., Shams-Ardakani, M., & Foroumadi, A. (2014). Medicinal plants in the treatment of *Helicobacter pylori* infections. *Pharmaceutical Biology*, *53*, 939–960. https://doi.org/10.3109/13880209.2014.952837

Saslis-Lagoudakis, C. H., Hawkins, J. A., Greenhill, S. J., Pendry, C. A., Watson, M. F., Tuladhar-Douglas, W., Baral, S. R., & Savolainen, V. (2014). The evolution of traditional knowledge: Environment shapes medicinal plant use in Nepal. *Proceedings of the Royal Society B: Biological Sciences*, *281*, 20132768. https://doi.org/10.1098/rspb.2013.2768

Saslis-Lagoudakis, C. H., Savolainen, V., Williamson, E. M., Forest, F., Wagstaff, S. J., Baral, S. R., Watson, M. F., Pendry, C. A., & Hawkins, J. A. (2012). Phylogenies reveal predictive power of traditional medicine in bioprospecting. *Proceedings of the National Academy of Sciences*, *109*, 15835–15840. https://doi.org/10.1073/pnas.1202242109

Saslis-Lagoudakis, C. H., Williamson, E. M., Savolainen, V., & Hawkins, J. A. (2011). Cross-cultural comparison of three medicinal floras and implications for bioprospecting strategies. *Journal of Ethnopharmacology*, *135*, 476–487. https://doi.org/10.1016/j.jep.2011.03.044

Schippmann U., Leaman D. J., & Cunningham A. B. (2002). *Impact of cultivation and gathering of medicinal plants on biodiversity: global trends and issues*. Rome: FAO: Inter-departmental Working Group on Biological Diversity for Food and Agriculture.

Shah, U., Shah, R., Acharya, S., & Acharya, N. (2013). Novel anticancer agents from plant sources. *Chinese Journal of Natural Medicines*, *11*, 16–23. https://doi.org/10.3724/sp.j.1009.2013.00016

Souza, E. N., Williamson, E. M., & Hawkins, J. A. (2018). Which plants used in ethnomedicine are characterized? Phylogenetic patterns in traditional use related to research effort. *Frontiers in Plant Science*, *9*, 834. https://doi.org/10.3389/fpls.2018.00834

Spjut, R. W., & Perdue, R. E. (1976). Plant folklore: A tool for predicting sources of antitumor activity? *Cancer Treatment Reports*, *60*, 979–985.

Staub, P. O., Geck, M. S., Weckerle, C. S., Casu, L., & Leonti, M. (2015). Classifying diseases and remedies in ethnomedicine and ethnopharmacology. *Journal of Ethnopharmacology*, *174*, 514–519. https://doi.org/10.1016/j.jep.2015.08.051

Taylor, T. B., Johnson, L. J., Jackson, R. W., Brockhurst, M. A., & Dash, P. R. (2013). First steps in experimental cancer evolution. *Evolutionary Applications*, *6*, 535–548. https://doi.org/10.1111/eva.12041

Teixidor-Toneu, I., Elgadi, S., Zine, H., Manzanilla, V., Ouhammou, A., & D'Ambrosio, U. (2021). Medicines in the kitchen: Gender roles shape ethnobotanical knowledge in Marrakshi households. *Food*, *10*, 2332. https://doi.org/10.3390/foods10102332

Teixidor-Toneu, I., Jordan, F. M., & Hawkins, J. A. (2018). Comparative phylogenetic methods and the cultural evolution of medicinal plant use. *Nature Plants*, *4*, 754–761. https://doi.org/10.1038/s41477-018-0226-6

Teixidor-Toneu, I., Kool, A., Greenhill, S. J., Kjesrud, K., Sandstedt, J. J., Manzanilla, V., & Jordan, F. M. (2021). Historical, archaeological and linguistic evidence test the phylogenetic inference of Viking-Age plant use. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *376*, 20200086. https://doi.org/10.1098/rstb.2020.0086

Thompson, J., Jordan, F., & Hawkins, J. (2022). Phylogenetic reconstructions of Polynesian medicinal plant use reveal adaptive strategies to meet health needs. https://doi.org/10.1101/2022.10.21.513211

Twarog, S., & Kapoor, P. (2004). *Protecting and promoting traditional knowledge systems, national experiences and international dimensions*. United Nations.

Verpoorte, R. (1998). Exploration of nature's chemodiversity: The role of secondary metabolites as leads in drug development. *Drug Discovery Today*, *3*, 232–238. https://doi.org/10.1016/s1359-6446(97)01167-7

Webb, C. O., Ackerly, D. D., & Kembel, S. W. (2008). PHYLOCOM: Software for the analysis of phylogenetic community structure and trait evolution. *Bioinformatics*, *24*, 2098–2100. https://doi.org/10.1093/bioinformatics/btn358

Wickham, H. (2011). GGPLOT2. *Wiley Interdisciplinary Reviews: Computational Statistics*, *3*, 180–185. https://doi.org/10.1002/wics.147

World Health Organization. Cancer. Available at: https://www.who.int/health-topics/cancer [Accessed April 11, 2023].

Yu, G., Smith, D. K., Zhu, H., Guan, Y., & Lam, T. T. (2016). ggtree: An r package for visualization and annotation of phylogenetic trees with

their covariates and other associated data. *Methods in Ecology and Evolution*, *8*, 28–36. https://doi.org/10.1111/2041-210x.12628

Zhou, X.-J., & Rahmani, R. (1992). Preclinical and clinical pharmacology of Vinca alkaloids. *Drugs*, *44*, 1–16. https://doi.org/10.2165/00003495-199200444-00002

Zhu, F., Qin, C., Tao, L., Liu, X., Shi, Z., Ma, X., Jia, J., Tan, Y., Cui, C., Lin, J., Tan, C., Jiang, Y., & Chen, Y. (2011). Clustered patterns of species origins of nature-derived drugs and clues for future bioprospecting. *Proceedings of the National Academy of Sciences*, *108*, 12943–12948. https://doi.org/10.1073/pnas.1107336108

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Thompson, J. B., & Hawkins, J. A. (2025). Phylogeny and bioprospecting: The diversity of medicinal plants used in cancer management. *Plants, People, Planet*, *7*(1), 147–158. https://doi.org/10.1002/ppp3.10566