Phylogeny, ethnomedicinal use and the distribution of phytoestrogens in the Fabaceae

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Introduction: Phytoestrogens, with estrogenic activity, are commonly found across the Fabaceae family. Here we develop methods that use phylogeny and ethnomedicinal information in order to identify candidate species for novel phytoestrogens.

Method: We selected Fabaceae species traditionally used as aphrodisiacs or with applications to control fertility (aphrodisiac-fertility species), to create a cross-cultural dataset of ethnomedicinal use. Using a phylogeny of the Fabaceae, "hot nodes" methods were used to identify lineages with a higher number of species with aphrodisiac-fertility uses. The known distribution of estrogenic flavonoids was used to determine whether the phytoestrogen-containing species was associated with aphrodisiac-fertility "hot nodes". Additionally, we examined the overlap of aphrodisiac-fertility uses with neurological applications, hypothesising that such species may have bioactive compounds with estrogenic properties. Lastly, the "aphrodisiac-fertility hot node" lineages without previously known estrogenic flavonoids were identified.

Results: We showed species in aphrodisiac-fertility hot nodes were more likely to contain estrogenic flavonoids (21% of species), a major group of phytoestrogens, compared to Fabaceae in the phylogeny (11% of species). Additionally, when aphrodisiac fertility species are limited to those with neurological applications, 62% of the species within hot nodes contain estrogenic flavonoids.

Discussion: We recognised 43 high-priority hot nodes, these lineages might represent promising targets for future studies on phytoestrogens. The results demonstrated the combining phylogenetic and ethnomedicinal data to guide the discovery of estrogenic flavonoids with therapeutic potential.

Introduction

Natural products continue to provide promising leads for drug discovery (Newman and Cragg, 2020). However, whether natural product research is practicable for drug discovery (Amirkia and Heinrich, 2015), and whether traditional uses in ethnomedicine can guide the discovery of new chemical compounds remains controversial (Gertsch, 2012; Gurib-Fakim, 2006; Saslis-Lagoudakis et al., 2011; Sucher, 2013; Skirycz et al., 2016). Devising strategies to target species for evaluation is an area of research interest (Fabricant and Farnsworth, 2001; Holzmeyer et al., 2020). Ethnobotanically-guided screening is one such approach (Fabricant

and Farnsworth, 2001). Strategies incorporating phylogenies alongside ethnobotanical use data have been adopted (Pellicer et al., 2018; Saslis-Lagoudakis et al., 2012; Souza et al., 2018). Here we apply phylogenetic methods to ethnobotanical use data, to explore whether they can more effectively target bioactive plant products.

Plant lineages that contain significantly more species with ethnomedicinal use were first referred to as hot nodes for bioprospecting by Saslis-Lagoudakis et al. (2011). Since then, hot nodes have been identified for different groups of medicinal plants from other parts of the world, and at varying taxonomic levels. At the generic level, hot nodes for potential anti-inflammatory compounds have been described for genus *Euphorbia* L. (Ernst et al., 2016), for species of interest to treat malaria in genus *Artemisia* L. (Pellicer et al., 2018), and for putative antioxidant and antidiabetic bioactivity for genus *Allium* L. (Teotia et al., 2024). At a higher taxonomic level, hot nodes in the orchid subtribe Coelogyninae that may show antimicrobial properties were identified based on ethnomedicinal uses (Wati et al., 2021). Geographically-focused studies have examined cross-cultural patterns between Nepal, South Africa and New Zealand (Saslis-Lagoudakis et al., 2012), whilst others have focused on the Brazilian Fabaceae (Souza et al., 2018), the Chinese Lamiaceae (Zaman et al., 2022) of whole medicinal floras (South Africa, Yessoufou et al., 2015; Atienza-Barthelemy et al., 2024), or pharmacopoeias (China, Zaman et al., 2021; India; Yao et al., 2023). Global studies include a study of angiosperms to identify hot nodes for psychoactive activity (Halse-Gramkow et al., 2016), for antimalarial properties (Milliken et al., 2021) and cancer (Thompson and Hawkins, 2024). Some of these studies have sought to validate the hot node method; for example, confidence in the hot node method is increased where hot nodes include a higher proportion of plant drugs in clinical trials (Ernst et al., 2016; Pellicer et al., 2018; Souza and Hawkins, 2017) or where there is cross-cultural convergence (Saslis-Lagoudakis et al., 2012). At least one study has used a literature search to show that hot node species have relevant biological activity (Teotia et al., 2024). Pellicer et al. (2018) screened for artemisinin in fifteen species, finding four of seven species from hot nodes and five of eight from outside hot nodes contained artemisinin. Their interpretation was that in this case–where a molecule of interest is common throughout the genus - the hot node approach is not effective. Given the increasing application of the hot node method, further tests of its validity are crucial.

Phytoestrogens (PE) are plant-derived compounds that have similar functions to estrogen. By binding to the estrogen receptor, estrogen (estradiol, E2) or PEs can activate estrogen-responsive genes, which in turn encode proteins that maintain bone, reproductive health, cognition, and cardiovascular function (O'Donnell et al., 2007; West et al., 2009). Consuming one common dietary source of PEs, soybean, can offer a range of health benefits, one of which is alleviating the symptoms of menopause (Branca and Lorenzetti, 2005). These symptoms include hot flashes, night sweats, vaginal dryness, mood changes, difficulty sleeping, anxiety and decreased libido (Booyens et al., 2022). Several medicinal plant drugs containing PEs are also used to reduce hot flashes and night sweats (Hajirahimkhan et al., 2013), vaginal dryness (Rosa Lima et al., 2014), and cardiovascular disease (Rossouw et al., 2007). The varying interactions of PEs with estrogen receptors suggest that different PEs may have specific functions or roles in various

tissues (Ceccarelli et al., 2022; Kiyama, 2022). Because PEs can have both therapeutic and cancer risks (Maggiolini et al., 2002; Umehara et al., 2008; Ye and Shaw, 2019), characterising the diversity of PEs to identify therapeutically optimal molecules is desirable. However, the studies of PEs for postmenopausal symptoms comprise a small number of plants. PEs appear to be distributed throughout the Fabaceae, though most plant sources remain uncharacterised, suggesting there are molecules yet unknown (Dixon, 2004; Rutz et al., 2022). Strategies to identify likely sources of novel PEs are therefore needed.

Here, we propose a strategy for identifying potential sources of therapeutically optimal, novel PEs for estrogen-related symptoms. A lack or excess of phytoestrogens, particularly from soybean-based foods, has been shown to suppress sexual behaviour development in both male and female rodents during puberty, suggesting that optimal concentrations of PEs can modulate estrogen-driven behaviours (Khan et al., 2008; Kudwa et al., 2007; Sandhu et al., 2020). Additionally, chemically isolated PEs such as genistein and daidzein have been shown to produce an anxiolytic-like effect in mice, indicating their potential role in reducing anxiety-related behaviours (Rodríguez-Landa et al., 2009; Zeng et al., 2010). The effects of PEs on socio-sexual behaviour may be mediated through a set of hypothalamic or hypothalamic-linked areas in the brain called the social behaviour network (SBN; Newman, 1999), and applications of plant drugs for neurological symptoms might affect the same regions (O'Donnell et al., 2007; West et al., 2009). Treatments for menopausal symptoms are very rarely described in ethnobotanical literature, but plants with hormone-modulating properties or those with estrogenic activity may be used as aphrodisiacs or to enhance fertility. Since these applications are directly relevant to sexual behaviour and are often well-documented in traditional medicine, we propose that the exploration of aphrodisiac fertility (AF) as a therapeutic category in ethnomedicine could highlight high-activity PEs that may act predominantly in the CNS. Additionally, neurological applications that regulate CNS activity (Dong and Nao, 2023) may intersect with these therapeutic uses, focusing on plants that have specific effects on the CNS. Species with AF use that also have neurological applications could therefore be of particular interest, as candidates for neuro-selective estrogens.

The Fabaceae is a large, widely distributed family comprising approximately 18,000 species, several of which are economically important for food and medicine (Lewis, 2005). Fabaceae plants are rich in alkaloids, flavonoids, saponins, tannins, glycosides, and other phytochemicals that contribute to their medicinal properties (Wink, 2013). Several studies show that the family Fabaceae is over-represented in medicinal floras (Moerman, 1991; Moutouama and Gaoue, 2024; Saslis-Lagoudakis et al., 2011). The species diversity, widespread distribution, and numerous reported uses (Souza and Hawkins, 2017)availability of phylogenetic information (Azani et al., 2017), and multiple reports of estrogenic compounds within this family (Kiyama, 2017; Kiyama, 2022) have motivated us to focus on this family.

The main objective of this study is to test whether phylogenetic methods may be useful to prioritise species for screening for PEs that could be therapeutically useful. A secondary objective is to identify and highlight candidate species that have not been the focus of research relevant to the identification of therapeutic PEs. Here we

identify species traditionally used for AF purposes and for closely related applications to enhance fertility, and that also have neurological applications. We test the hypothesis that hot nodes identified using ethnomedicinal data include more species known to have PEs than a random sample. The distribution of PEs was according to a database of natural products, the LOTUS database (Rutz et al., 2022). We suggest that the phylogenetic analyses can highlight ethnomedicinally important lineages that are putative sources of novel PEs.

Methods

Data collection

Species-level data for flowering plants used as medicine were gathered from recent and comprehensive systematic reviews for Brazil (Souza et al., 2018), China (Zaman et al., 2021), the Greco-Roman Mediterranean (Leonti et al., 2024), the sub-Saharan region of Africa (Ajao et al., 2019) and Thailand (Phumthum et al., 2018).

We compiled a list of aphrodisiac-fertility (AF) species in Fabaceae from these sources by using the search terms "aphrodisiac," "sexual intercourse," "libido," "fertility," and "sterilisation." AF plants are those that stimulate sexual desire. Aphrodisiac use refers to sexual desire within the psychological category. However, aphrodisiacs have also been used in other categories, such as fertility, erectile dysfunction, menstrual disorders, and pregnancy, which fall under the genital system and pregnancy categories. For a more extensive search, we included fertility properties in the search terms because sexual desire and fertility are related to each other (Berger et al., 2016) and estrogen and PEs affected both sexual desire and fertility (Najaf Najafi and Ghazanfarpour, 2018; Scavello et al., 2019).

Whether the species with AF use had other therapeutic uses was recorded from the original sources and by Google Scholar and PubMed searches. Other uses were classified into ten therapeutic applications (general, blood, digestive, eye, circulatory, muscular, neurological, psychological, respiratory, skin, nutritional, and urinary) according to the ICPC-3 International Classification of Primary Care (van Boven and Ten Napel, 2021).

The list of known PEs (Supplementary Material S1), particularly flavonoids, was obtained by referencing a review on estrogenic flavonoids (Kiyama, 2022). These compounds were then cross-referenced with the LOTUS initiative database, a database which includes 750,000 referenced structure-organism pairs (Rutz et al., 2022). We used "stringdist_left_join" function from the "fuzzyjoin" package with a maximum difference of two characters between words in R (Robinson et al., 2020) to extract Angiosperm species containing estrogenic flavonoids (Supplementary Material S2).

Phylogenetic analysis

We utilised a large time-calibrated phylogeny of the rosids comprising nearly 20,000 species (Sun et al., 2020), and pruned it to retain only the species in Fabaceae from our data using the "keep.tip" function from the "ape" package in R (Paradis et al., 2004). The final phylogeny included 5,626 (31%) of approximately 18,000 Fabaceae species and 651 (85%) of the 765 Fabaceae genera. We used this phylogeny, the list of AF species and the list of species with estrogenic flavonoids in our analyses.

The D statistic was calculated as an estimate of the phylogenetic signal of the AF species using the "phylo.d" function from the "caper" package in R (Fritz and Purvis, 2010).

We predicted the hot nodes for AF use at the species level using the "hot.nodes" function developed by (Molina-Venegas et al., 2020). Hot nodes were considered only if they contained fewer than 100 species, following (Halse-Gramkow et al., 2016). Hot nodes were recognised according to the number of species within the lineage, rather than across the entire genus where genera were split between nodes. To determine whether screening known AF species or species that belong to AF hot nodes is an efficient bioprospecting strategy, we calculated the percentage of known estrogenic flavonoids by the species that belonged to these groups. These percentages were compared to the overall percentages of species in the family known to contain estrogenic flavonoids, as well as to the percentage of species within the phylogeny that possess estrogenic flavonoids. We refer to these percentages as "search efficiency" (Souza et al., 2018).

We supposed that those AF hot nodes that contained no known estrogenic flavonoids might be the sources of novel estrogenic flavonoids, and made species lists for these nodes.

The predicted lineages, hot nodes and the phylogenetic distributions of species containing estrogenic flavonoids were visualised using the Interactive Tree of Life v5 (Letunic and Bork, 2021).
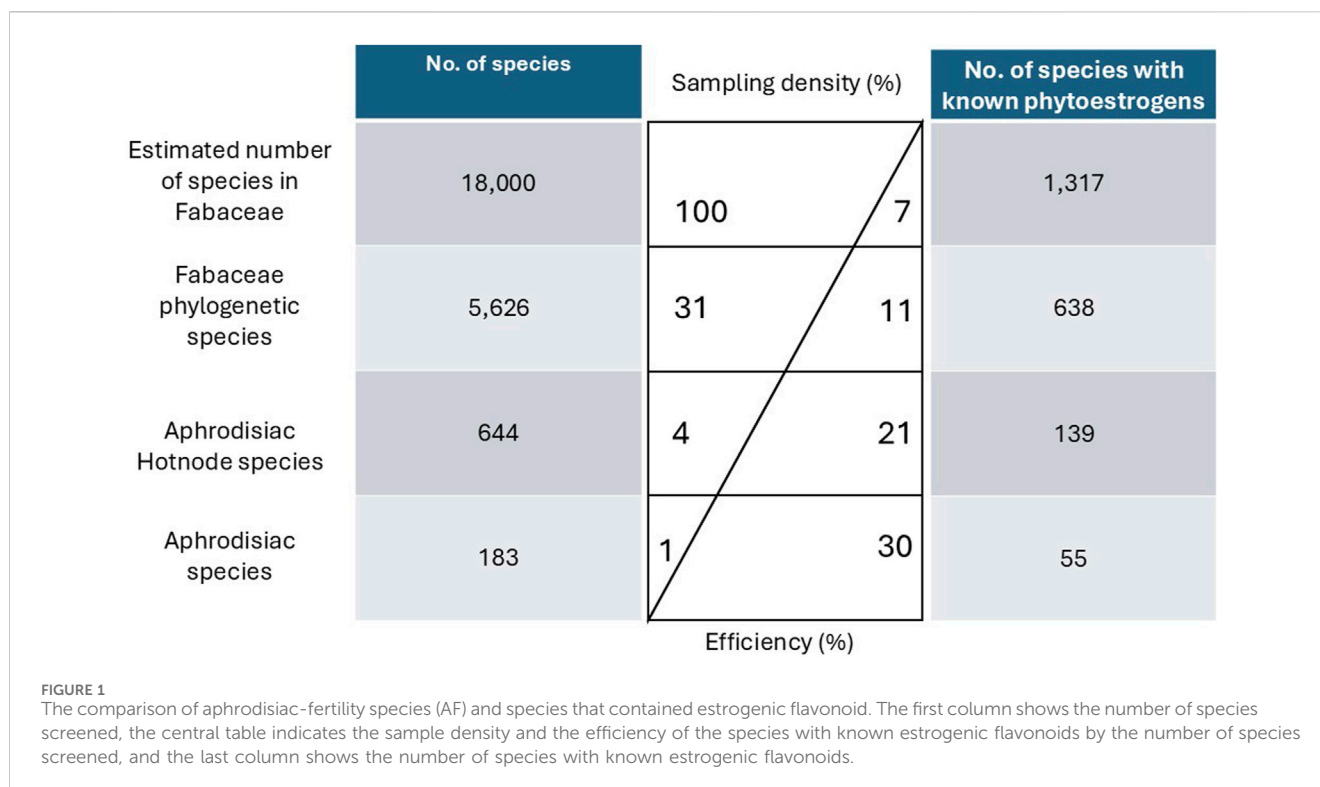
Results

AF species and species with known estrogenic flavonoids

According to the five sources, 183 species belonging to 64 genera were the source of AF medicines. Eight were from Brazil, 122 were from China, seven were from the Graeco-Roman Mediterranean, 28 were sub-Saharan, and 19 were from Thailand (Supplementary Material S3). We were able to identify 638 species that were recorded to produce estrogenic flavonoids, showing approximately 11% of the 5,626 species of Fabaceae phylogeny are known to produce estrogenic flavonoids (Supplementary Material S3). Fifty-five (30%) of the species used as AFs were known to have estrogenic flavonoids, and these represented 35 genera; we consider screening AF species to have 30% efficiency (Figure 1).

Predicting lineages with elevated bioprospecting potential

Of the 183 AF species, 106 (57%) were included in the phylogeny. The estimated D statistic for these species was 0.70, indicating a weak to moderate phylogenetic signal for the AF trait. The "hot.nodes" function identified 319 AF hot nodes. AF hot nodes are nested, so our analysis identified 43 highest-level AF hot nodes (Figure 2). These 43 hot nodes comprise 644 species in 142 genera, of which 139 species were known to contain estrogenic flavonoids

FIGURE 1
The comparison of aphrodisiac-fertility species (AF) and species that contained estrogenic flavonoid. The first column shows the number of species screened, the central table indicates the sample density and the efficiency of the species with known estrogenic flavonoids by the number of species screened, and the last column shows the number of species with known estrogenic flavonoids.

(21% efficiency; Figure 1). The average number of species in the higher-level AF hot nodes was 29.86 ± 52.27. Of the 43 AF hot nodes, there were 12 that did not include any species known to have estrogenic flavonoids according to the LOTUS initiative database; the average number of hot node species known to have estrogenic flavonoids was 11.49 species, with a standard deviation of 31.77.

Of the 43 highest-level hot nodes, 31 correspond to species known to contain estrogenic flavonoids (Table 1, Supplementary Material S4). There were 12 that did not include any species known to contain estrogenic flavonoids, Table 2 shows these AF hot nodes. The number of species in them ranges from two to 25, with two of the smallest AF hot nodes only including two species, and one node has three species. The first hot node was a sub-family of *Dialioideae* Legume Phylogeny Working Group, and the third cluster contained the genus *Delonix* Raf. The sixth and seventh clusters were in the genera *Vachellia* Wight and Arn., and the eighth cluster included *Senegalia* Raf. and relatives. The ninth cluster was in the genus *Poiretia* Sm. The 10th and 11th clusters were in the genus *Indigofera* L., while the last cluster was in the genus *Sesbania* Adans.

Neurological applications of AF plants

There were 18 of the 165 AF species (10.9%) that also had neurological applications. Of these 18 species, 13 were found in the AF hot nodes, and of those 13, there were eight species (62%) that have been shown to contain estrogenic flavonoids. The eight plants were *Peltophorum africanum* Sond, *Senna siamea* (Lam.) H.S.Irwin and Barneby, *Senna petersiana* (Bolle) Lock, *Mundulea sericea* (Willd.) A. Chev., *Abrus precatorius* L., *Glycyrrhiza glabra* L., *Vicia sativa* L., and *Mimosa pudica* L. In comparison, only 22%

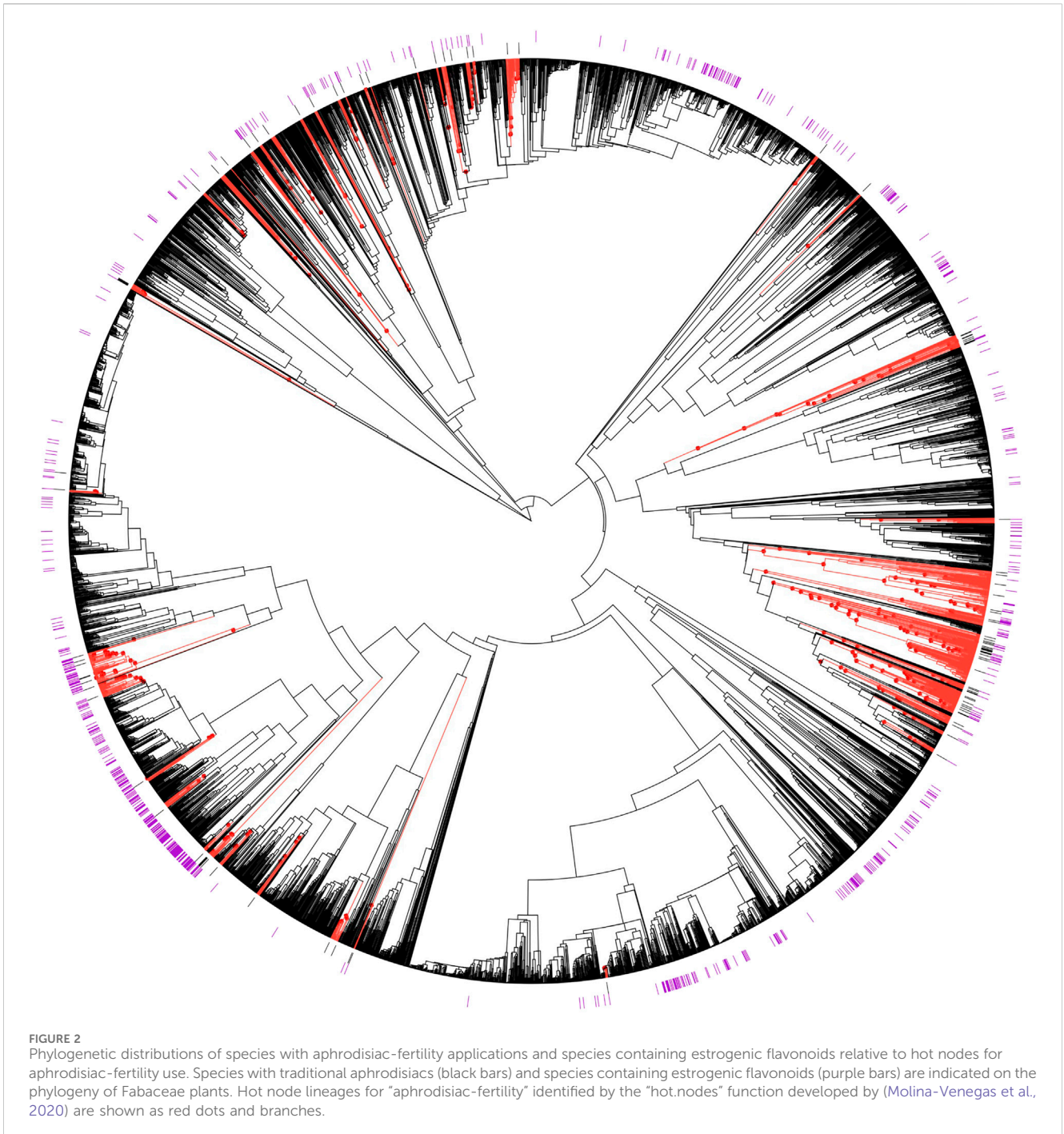of the 165 AF species without neurological applications found estrogenic flavonoids.

The frequency of other therapeutic applications of the AF medicinal plants is shown in Figure 3. 40 AF plants were used to treat "general" disorders, so this was the most common category of use for AF. The second most common category was "digestive" disorders; the "neurological" categories were the next most frequently cited, with 19 AF species reported as used for disorders in each of these categories.

Discussion

The efficiency of phylogenetic prediction

Species with aphrodisiac and fertility uses appear good candidates for the discovery of novel estrogenic flavonoids. A major challenge in drug discovery from plants is the need to select strategically which species to screen, given the impracticality of evaluating all species (Verpoorte, 2000). Plant-derived drugs have been discovered through random or systematic screening of local floras (Perdue and Hartwell, 1969; Spjut, 1985; Barclay and Perdue Jr, 1976) and therapeutic applications in ethnomedicine have also been used in screening programmes to discover new drug leads for many decades. Optimisation of the screening process could include focusing on ethnomedicinal species or plant lineages to which they most frequently belong. This study focused on plants with aphrodisiac and fertility applications in the context of phylogeny to predict lineages with estrogenic flavonoids. Even before we incorporated a phylogenetic framework and hot node analysis, we found that 30% of AF species produce estrogenic

FIGURE 2
Phylogenetic distributions of species with aphrodisiac-fertility applications and species containing estrogenic flavonoids relative to hot nodes for aphrodisiac-fertility use. Species with traditional aphrodisiacs (black bars) and species containing estrogenic flavonoids (purple bars) are indicated on the phylogeny of Fabaceae plants. Hot node lineages for "aphrodisiac-fertility" identified by the "hot.nodes" function developed by (Molina-Venegas et al., 2020) are shown as red dots and branches.

flavonoids, compared to 11% of species in phylogenetic tree, demonstrating an increased frequency of estrogenic flavonoid-containing species amongst species with AF applications.

Our study reported a D statistic of 0.70, which is a weak to moderate phylogenetic signal for the AF trait (Fritz and Purvis, 2010). However, our community phylogenetic statistics highlighted a pattern of "clusters," since both MPD and MNTP are positive, encouraging us to explore the distribution of estrogenic flavonoids relative to hot nodes for the AF trait. The D statistic is rarely reported in studies of specific therapeutic applications, but one example also includes weak to moderate values: in the genus

Euphorbia L. D statistic values were all weak apart from one moderate value (Ernst et al., 2016). Our finding, that 21% of species in AF hot nodes have estrogenic flavonoids compared to 11% overall, appears to validate the hot node method, even though the D statistic was suggestive of only moderate predictive power. The search efficiency of 21% for screening hot node species is lower than the search efficiency of 30% for the direct screening of AF species. However, hot node species represent more than three times as many candidates for screening without a correspondingly large decrease in known estrogenic flavonoids. We propose that, at least in the case of the Fabaceae, screening hot node species as well as ethnomedicinal

TABLE 1 The well-characterized species from aphrodisiac-fertility hot nodes corresponded with estrogenic flavonoids in the LOTUS Initiative database (Rutz et al., 2022) and their bioactivities. The species were selected based on the highest number of estrogenic flavonoids identified in the LOTUS Initiative database, excluding species within the same genus.

Species	Estrogenic-flavonoids	Bioactivities
Glycyrrhiza glabra L.	Glabrene, Licochalcone a, Galangin, Formononetin, Pinocembrin, Glabridin, Hispaglabridin A, Glabrol, Rutin, Hispaglabridin B, Isobavachromene, Isoliquiritigenin, Naringenin, Genistein, Astragalin, Prunetin, Liquiritigenin, Glyasperin C, Isobavachalcone, Medicarpin, Glycycoumarin, Wighteone, Afrormosin, and Phaseolin.	Antioxidant, Anti-inflammatory, Antitussive and Expectorant, Antiulcerative, Antimicrobial, Antiviral, Hepatoprotective, Anticarcinogenic, Antimutagenic, Neuroprotective, Sedative, and Antidepressive (Pastorino et al., 2018)
Phaseolus vulgaris L.	Rutin, Coumestrol, Kaempferol, Quercetin, Astragalin, Vestitone, Pelargonidin, Cianidanol, Kievitone, Luteolin, Genistein, Phaseolin, Daidzein, L-Epicatechin, Taxifolin, Apigenin, Naringenin, Myricetin, Delphinidin 3-glucoside, Hesperetin, and Cyanidin, Pelargonidin 3-glucoside.	Immunogenicity, Anticarcinogenic, Antiviral, Antimicrobial, Cardioprotective, Antidiabetic, and Anti-obesity (He et al., 2018; Rodríguez et al., 2022; Peddio et al., 2022)
Glycine max (L.) Merr.	Kaempferol, Daidzein, Formononetin, Genistein, Coumestrol, Naringenin, Glyceollin, Glycitein, Quercetin, Isoliquiritigenin, Cianidanol, Rutin, Afrormosin, Fisetin, Glyceollidin II, Isoformononetin, Astragalin, and Glyceollin II, Vitexin.	Estrogenic, Anti-estrogenic, Anti-thrombotic, Postmenopausal Relief, Antimutagenic, Antihypertensive, Antioxidant, Neuroprotective, Immunoregulatory, Anticancer, Anti-obesity, and Anti-arteriosclerosis (Rizzo and Baroni, 2018; Cao et al., 2019; Kim et al., 2021)
Pueraria montana (Lour.) Merr.	Coumestrol, Formononetin, Tectoridin, Daidzein, Glycitein, Tectorigenin, Kakkalide, Genistein, Isoliquiritigenin, Isoformononetin, Sissotrin, Irisolidone, Apigenin, Quercetin, Baicalein, and Medicarpin.	Anti-alcoholism, Antioxidant, Hepatoprotective, Antidiabetic, Neuroprotective, Cardioprotective, Nephroprotective, Anti-inflammatory, Mutagenic, Anticancer, Antibacterial, and Anti-osteoporosis (Wang et al., 2020)
Cicer arietinum L.	Calycosin, Pratensein, Sissotrin, Genistein, Formononetin, Quercetin, Vestitone, Daidzein, Garbanzol, Astragalin, Isorhamnetin, Medicarpin, Cianidanol, Naringenin, Isoliquiritigenin, and Kaempferol.	Antioxidant, Antitumor, Antiproliferative, Anti-inflammatory, and Antibacterial (Wang et al., 2021)
Cullen corylifolium (L.) Medik.	Corylifol A, Neobavaisoflavone, Psoralidin, Bavachin, Daidzein, Bavachalcone, Coumestrol, Corylin, Bavachinin, Isobavachalcone, Isobavachromene, Genistein, Isobavachin, and Astragalin.	Anti-osteoporosis, Antitumor, Antiviral, Antibacterial, Anti-inflammatory, Anticancer, Anti-vitiligo, and Antidepressant-like (Qi et al., 2023; Ren et al., 2020; Sharifi-Rad et al., 2020)
Butea monosperma (Lam.) Kuntze	Genistein, Formononetin, Prunetin, Butin, Cajanin, Butein, Daidzein, Medicarpin, Isoliquiritigenin, Liquiritigenin, Afrormosin, Isoformononetin, and Kaempferide.	Antibacterial, Antiviral, Anticancer, Anti-inflammatory, Antioxidant, and Neuropathic Pain Relief (Forouzanfar and Hosseinzadeh, 2018; Hiremath et al., 2024)
Vicia faba L.	Neohesperidin dihydrochalcone, Kaempferol, Cyanidin, Astragalin, Formononetin, Myricetin, Luteolin, Cianidanol, Butein, Apigenin, Chrysoeriol, and Quercetin.	Antioxidant, Antidiabetic, Cholesterol-lowering, Anti-inflammatory, Anticancer, Antihypertensive, and Antimicrobia (Martineau-Côté et al., 2022)
Andira inermis (W.Wright) Kunth ex DC.	Engeletin, Formononetin, Taxifolin, Afrormosin, Pratensein, Calycosin, Astilbin, Prunetin, Genistein, and Daidzein.	Hypoglycemic, Antioxidant, Hematological, and Antiplasmodial (Egua et al., 2020; Gayus Aminu et al., 2024)
Spatholobus suberectus Dunn	Liquiritigenin, Formononetin, Genistein, Daidzein, Calycosin, Afrormosin, Taxifolin, Butin, and Butein	Neuroprotective, Antioxidant, Antitumor, Antiviral, Antidiabetic, and Anti-inflammatory (Huang et al., 2023; Zhang et al., 2022)
Trigonella foenum-graecum L.	Luteolin, Kaempferol, Rutin, Daidzein, Formononetin, Astragalin, Calycosin, Quercetin, and Irilone.	Antimicrobial, Anticancer, Antioxidant, Neuroprotective, Hormonal, and Anti-obesity (Visuvanathan et al., 2022)
Flemingia macrophylla (Willd.) Kuntze ex Merr	Lupinalbin A, Genistein, Kushenol E, Auriculasin, Prunetin, 6,8-Diprenylorobol, Flemiphilippinin C, Flemiphilippinin A, and Flemichin D.	Antioxidant, Antityrosinase, and Antidiabetic (Gahlot et al., 2013; Wang et al., 2012; Fatema et al., 2024)
Vigna radiata (L.) R.Wilczek.	Kaempferol, Quercetin, Formononetin, Astragalin, Kievitone, Daidzein, Rutin, and Genistein.	Hypoglycemic, Hypolipidemic, Hepatoprotective, Antihypertensive, Anticancer, Immunomodulatory, and Anti-melanogenesis (Hou et al., 2019)

species is strategic. Accessing species in sufficient quantity for screening is not trivial, so being able to have more than three times as many candidates without a correspondingly large decrease in the identification of species with PEs would be valuable.

In this study, we show that considering the overlap between a pair of therapeutic applications can enhance the effectiveness of phylogenetic search strategies. The second application we explore here is the application for neurological therapeutic needs. Our data show that when AF applications overlap with neurological uses, these plants are more likely to include estrogenic flavonoids, suggesting a potential dual role in both reproductive and

neurological health. We found that 62% of the AF species that are found in hot nodes and that have neurological applications are known to contain estrogenic flavonoids. This is markedly higher than the 22% with phytoestrogens found among the 165 AF species alone. Considering the other therapeutic applications of the AF species, we show that use for neurological disorders is the second most common specific application, after digestive applications. This appears to be an elevated frequency, for example, in comparison to a ranking of ninth in a study of all therapeutic applications of Brazilian Fabaceae (Souza and Hawkins, 2017), further supporting the view that neurological and AF applications highlight plants with similar

TABLE 2 The clusters of hot nodes that include no species recorded as having estrogenic flavonoids in the LOTUS initiative database (Rutz et al., 2022). High-level hot nodes were named by tribe or by most represented genus. If a hot node is repeated in another named node, the descendant node is named alphabetically by the genus appearing first.
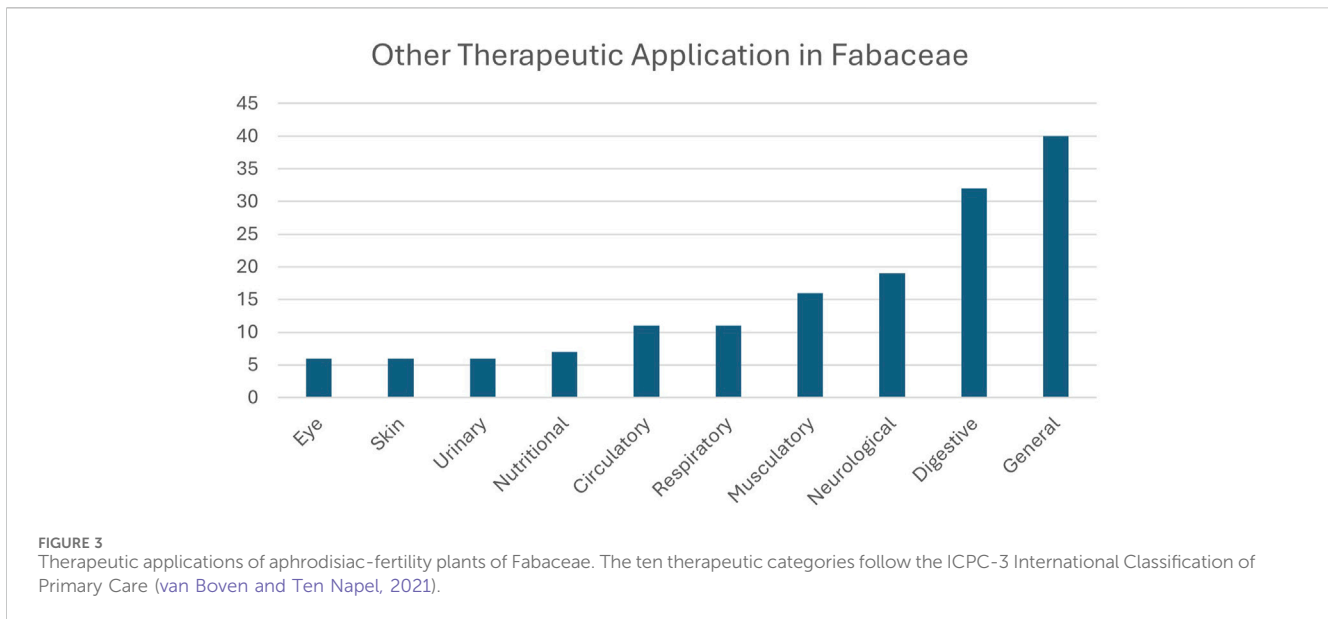
High-level hot nodes	Number of nested hot nodes	Species
1. Dialioideae nodes	4	*Apuleia leiocarpa* (Vogel) J.F.Macbr., *Dialium guineense* Willd., *Dicorynia guianensis* Amshoff, *Distemonanthus benthamianus* Baill., *Koompassia excelsa* (Becc.) Taub., *Labichea punctata* Benth., *Martiodendron parviflorum* (Amshoff) Köppen, *Storckiella australiensis* J.H.Ross and B.Hyland, *Petalostylis labicheoides* R.Br., and *Zenia insignis* Chun
2. *Clitoria* node	1	*Chamaecrista acosmifolia* (Mart. Ex Benth.) H.S.Irwin and Barneby, and *Clitoria guianensis* (Aubl.) Benth.
3. *Delonix* nodes	3	*Colvillea racemosa* Bojer, *Delonix boiviniana* (Baill.) Capuron, *D. brachycarpa* (R.Vig.) Capuron, *D. edulis* (H.Perrier) Babineau and Bruneau., *D. elata* (L.) Gamble, *D. floribunda* (Baill.) Capuron, *D. pumila* Du Puy, Phillipson and R.Rabev., *D. regia* (Bojer ex Hook.) Raf.[a], and *D. velutina* Capuron
4. *Entada* node	1	*Entada elephantina* (Burch.) S.A.O'Donnell and G.P.Lewis, and *E. abyssinica* Steud. Ex A.Rich.
5. *Alantsilodendron* node	1	*Alantsilodendron pilosum* Villiers, *Dichrostachys spicata* (F.Muell.) Domin, and *Vachellia nilotica* (L.) P.J.H.Hurter and Mabb.
6. *Vachellia borleae* nodes	5	*Vachellia borleae* (Burtt Davy) Kyal. and Boatwr., *V. dyeri* (P.P.Sw. Ex Coates Palgr.) Kyal. and Boatwr., *V. flava* (Forssk.) Kyal. and Boatwr., *V. karroo* (Hayne) Banfi and Galasso[a], *V. kirkii* (Oliv.) Kyal. and Boatwr., *V. leucophloea* (Roxb.) Maslin, Seigler and Ebinger, and *V. robbertsei* (P.P.Sw. Ex Coates Palgr.) Kyal. and Boatwr.
7. *Vachellia caven* nodes	3	*Neltuma laevigata* (Humb. and Bonpl. Ex Willd.) Britton and Rose, *Vachellia caven* (Molina) Seigler and Ebinger, *V. bravoensis* (Isely) Seigler and Ebinger, *V. etbaica* (Schweinf.) Kyal. and Boatwr., *V. farnesiana* (L.) Wight and Arn., and *V. schaffneri* (S.Watson) Seigler and Ebinger.
8. *Senegalia* nodes	7	*Acacia pulchella* R.Br., *A. scleroxyla* Tussac, *Senegalia burkei* (Benth.) Kyal. and Boatwr., *S. caffra* (Thunb.) P.J.H.Hurter and Mabb., *S. dudgeonii* (Craib) Kyal. and Boatwr., *S. erubescens* (Welw. Ex Oliv.) Kyal. and Boatwr., *S. ferruginea* (DC.) Pedley, *S. fleckii* (Schinz) Boatwr., *S. galpinii* (Burtt Davy) Seigler and Ebinger, *S. goetzei* (Harms) Kyal. and Boatwr., *S. hereroensis* (Engl.) Kyal. and Boatwr., *S. laeta* (R.Br. Ex Benth.) Seigler and Ebinger, *S. macrostachya* (Rchb. Ex DC.) Kyal. and Boatwr., *S. mellifera* (Vahl) Seigler and Ebinger, *S. modesta* (Wall.) P.J.H.Hurter, *S. nigrescens* (Oliv.) P.J.H.Hurter, *S. polyacantha* (Willd.) Seigler and Ebinger, *S. robynsiana* (Merxm. and A.Schreib.) Kyal. and Boatwr., *S. senegal* (L.) Britton, *S. welwitschii* (Oliv.) Kyal. and Boatwr., *Parasenegalia muricata* (L.) Seigler and Ebinger, *P. vogeliana* (Steud.) Seigler and Ebinger, *Prosopis cineraria* (L.) Druce, and *Vachellia sieberiana* (DC.) Kyal. and Boatwr.
9. *Poiretia* nodes	1	*Poiretia angustifolia* Vogel, *P. latifolia* Vogel, *P. punctata* (Willd.) Desv., and *P. tetraphylla* (Poir.) Burkart
10. *Indigofera amblyantha* nodes	6	*Indigofera amblyantha* Craib, *I. cassioides* Rottler ex DC., *I. cylindracea* Graham ex Baker, *I. decora* Lindl., *I. dosua* Buch.-Ham. ex D.Don, *I. grandiflora* B.H.Choi and S.K.Cho, *I. hebepetala* Benth. Ex Baker, *I. heterantha* Wall. Ex Brandis, *I. himalayensis* Ali, *I. kirilowii* Palib, *I. koreana* Ohwi, *I. lacei* Craib, *I. nigrescens* Kurz ex King and Prain, *I. pendula* Franch., *I. thibaudiana* DC. and *I. venulosa* Champ. Ex Benth.
11. *Indigofera bemarahaensis* nodes	5	*Indigofera bemarahaensis* Du Puy and Labat, *I. exellii* Torre, *I. glandulosa* J.C.Wendl., *I. leucoclada* Baker, *I. squalida* Prain, *I. prostrata* Willd., and *I. psoraloides* (L.) L.
12. *Sesbania* nodes	4	*Sesbania campylocarpa* (Domin) N.T.Burb., *S. bispinosa* (Jacq.) W.Wight, *S. brachycarpa* F.Muell., *S. formosa* (F.Muell.) N.T.Burb., *S. grandiflora* (L.) Poir., *S. microphylla* Harm., and *S. transvaalensis* J.B.Gillett

[a]Neurological uses.

bioactivity. Here we highlight the two AF hot nodes which meet the criteria of hot-node inclusion and neurological use, but which have not been tested for estrogenic flavonoids: *Delonix* nodes and *Vachillia borleae* nodes. A literature survey revealed two species, one from each hot node, *Delonix regia* (Bojer ex Hook.) Raf. and *Vachellia karroo* (Hayne) Banfi and Galasso, which did contain estrogenic flavonoids. *Delonix regia* (Bojer ex Hook.) Raf. contains quercetin and its derivatives (Modi et al., 2016) and *V. karroo* (Hayne) Banfi and Galasso has epicatechin (Maroyi, 2017); both are estrogenic flavonoids (Kiyama, 2022). Neither species was included in our list of estrogenic flavonoid species because the natural product database was incomplete (Rutz et al., 2022). Our study shows that

the database has been sufficient to validate the use of the AF category in hot node analysis. Going forward, it is likely that analyses of this kind for other flowering plant families would use the LOTUS initiative database, as it is a current and freely available resource.

In our study, we use knowledge of whether plants have estrogenic flavonoids to show that ethnomedicinal uses have predictive power. The presence of estrogenic-flavonoid compounds (Kiyama, 2022) was determined using the LOTUS initiative database (Rutz et al., 2022). Other studies which have sought to validate the hot node method have made comparisons to plant drugs in clinical trials (Pellicer et al., 2018; Ernst et al., 2016; Souza and Hawkins, 2017). Given the increasing application of the

FIGURE 3
Therapeutic applications of aphrodisiac-fertility plants of Fabaceae. The ten therapeutic categories follow the ICPC-3 International Classification of Primary Care (van Boven and Ten Napel, 2021).

hot node method, validation is crucial, so a critical consideration of assumptions related to validation is important. The increase in "search efficiency" we find, from 11% to 30%, is interpreted here as the power of traditional medicine in phytochemical prediction. However, it could also represent a screening bias. There are several biases that one should be aware of, and that might suggest caution in the interpretation of studies such as ours.

Species distributions follow a hollow curve, with some species being highly abundant whilst most are relatively rare (McGill et al., 2007). Widespread species are more likely to be recognised for their properties and included in local medicinal floras, because of both their accessibility and visibility in ethnobotanical field studies (Stepp and Moerman, 2001). For instance, 26% of North American weedy species were reported to have ethnomedicinal use, compared to only 8% of native flora (Moerman, 2005). Furthermore, the species that are used in ethnomedicine may be more likely to be screened because of their perceived value and because they are easily accessible species, contributing to a sampling bias favouring common, weedy species. The size of the genus may also influence research screening effort. Spjut (1985) observed that most genera were represented by only one or two species in screening efforts, whereas the majority of screened species came from large genera distributed across both tropical and temperate phytogeographic regions. While widespread species are better studied and more frequently reported, rare species often remain undocumented, and indigenous perceptions—critical to ethnomedicine—cannot be fully quantified (Phillips and Gentry, 1993). It might be argued that an elevated percentage of species known to have PEs in a hot node, relative to the percentage in the family as in tree, could be because a large proportion of the species in the family are not studied because they are rare. The elevated proportion in the hot nodes would therefore be because there are more ethnobotanically-used species which are screened more often, both because of their medicinal uses and because they are widespread. More sophisticated models are needed to consider the distribution of plants. However, whilst we recognise this caveat, we do consider the raised search efficiency to validate our method. Three factors in addition to the

elevated frequency of species with known PEs are relevant here. Firstly, there is an elevated frequency of a secondary therapeutic application, neurological application, and we had predicted these two uses would be attributed to the same underlying phytochemistry. Secondly, our hot node data are drawn from a cross-cultural sample. This is important because it allows us to discover lineages independently, where cultural beliefs about virility might result in biases in studies of a single culture. Such culture-specific beliefs might be expected for aphrodisiac application, for example, it is well known that bitter tonics are attributed aphrodisiac properties specifically in West Africa and the Caribbean (van Andel et al., 2012). Thirdly, we did find that there were PEs in species we predicted to have them, even when these were not recorded by the LOTUS initiative database. Ultimately, the strongest test of the method may be to assay the plants. Pellicer et al. (2018) screened for artemisinin in fifteen species but did not find that species from hot nodes were significantly more likely to have this bioactive molecule. Whether this is an issue specific to congeneric species, where the biosynthetic pathways needed to produce a bioactive are shared, will be determined by further tests of this kind.

We show that predictive methods of the kind we carry out here merit further investigation. However, the search for therapeutically relevant small molecules has ethical dimensions. The data we analyse here are publicly available data describing ethnomedicinal plant use. Much of these data are available as the result of ethnobotanical research, perhaps motivated by a perceived need to preserve ethnomedicinal knowledge that was experiencing rapid erosion (McManis and Ong, 2018; Schultes, 2007). The ethical dimensions of placing data in the digital commons are now under scrutiny (Mulatinho Simoes and Birchfield, 2024). Where research in this area is carried out by national programmes, in China and India, for example, the twin aims of validating and preserving traditional medicine systems can be met, whilst any commercial benefits remain in-country. In our study, the data that we use comes from multiple cultures, and species are highlighted that may not have documented, relevant traditional use. Pellicer et al. (2018) recognise this as an ethical

"grey area" yet not addressed and we further highlight this issue here.

Whether the ethical dimensions of the kind of analysis we present here become the specific focus of rethinking protections for knowledge holders may depend on whether these methods enter the commercial sphere. At present, to the best of our knowledge, work of the kind we present here remains in the academic literature. However, the hot node approach has the advantage of highlighting a broader range of species within the same lineage as known ethnobotanical species. While easily accessible AF plants have been well-characterized in local and regional studies (Ajao et al., 2019; Ganie et al., 2019). Other AF plants remain understudied, perhaps due to the limited availability of plant material. These local and regional studies of local plants could include screening of species that are not used medicinally but that are highlighted by phylogenetic studies. In this way, hot node studies use global data to highlight locally available species to incorporate into local and regional research. Hot nodes provide a better way of identifying species that are a random selection, thus reducing unproductive screening in national programmes.

Even where a wider number of species might be targeted, practical limitations such as the season-dependent chemical composition of plant material, which restrict the time window for recollection, remain. Although many plant-derived natural products have already been isolated and characterized, the amounts available were usually insufficient for extensive testing across a wide range of biological activities (Atanasov et al., 2015). In addition to the accessibility of plant material, the quality was also important. The available plant material often varied in quality and composition, which could hinder the accurate assessment of its therapeutic claims. Chemical composition was influenced not only by species identity and harvest time but also by factors such as soil composition, altitude, climate, processing, and storage conditions (Atanasov et al., 2015). Furthermore, during extraction and isolation processes, compounds could transform and degrade, further complicating the evaluation of their potential therapeutic benefits (Kingston, 2011). These challenges in devising and implementing a screening programme highlight how important it may be to widen the pool of targeted species.

Ethnobotany and phytochemistry of priority AF hot nodes

This study devised, tested and demonstrated the utility of a method to use aphrodisiac-fertility AF hot nodes to discover PEs. To demonstrate that the method works, we have necessarily focused on a plant family that has been well-studied, so the distribution of PEs is well-known. Nevertheless, we identified AF hot nodes that did not include any species known to contain estrogenic flavonoids according to the LOTUS initiative database. These priority AF hot nodes were investigated in more detail, and several were shown to include estrogenic flavonoids.

The **Dialioideae** nodes include *Apuleia leiocarpa* (Vogel) J.F.Macbr., the bark of this species was used in Peru as a drug to help expel the placenta during childbirth (Odonne et al., 2013), and the root bark of *Distemonanthus benthamianus* Baill. was used for pain relief (Ajibesin et al., 2008). Phytochemical studies of *A.

leiocarpa (Vogel) J.F.Macbr. have revealed the presence of flavones (Braz Filho and Gottlieb, 1971), although their estrogenic activities have not yet been investigated.

The **Delonix** nodes include trees native to Madagascar and East Africa. The most well-known species of the twelve species in the genus, *D. regia* (Bojer ex Hook.) Raf., has been used in traditional medicine globally and extensively studied for its phytochemical properties (Modi et al., 2016). Ethnobotanical reports show that its flowers have been used to treat gynaecological disorders (Vidyasagar and Prashantkumar, 2007). Studies have identified flavonoids such as leucocyanidin, cyanidin, and quercetin and their derivatives in the plant (Adjé et al., 2010). Another species, *Delonix elata* (L.) Gamble, has been researched for its mosquito-repellent properties (Govindarajan et al., 2015). While *D. regia* (Bojer ex Hook.) Raf. and *D. elata* (L.) Gamble have been extensively studied, other species within the genus have received less attention.

The genera **Acacia**, **Senegalia**, and **Vachellia** are found in the *Vachellia borleae* nodes, *Vachellia caven* nodes, and *Senegalia* nodes, and were previously grouped as a single genus that was segregated due to its non-monophyly (Kyalangalilwa et al., 2013). These genera are found in Australia, Africa, and other tropical regions (Maslin et al., 2003), and have been widely used in traditional medicine across these areas. Phytochemical investigations have identified flavonoids such as apigenin, catechin, epicatechin, kaempferol, naringenin, quercetin, and myricetin derivatives in species from both Africa and Australia (Subhan et al., 2018). One species, *Vachellia nilotica* (L.) P.J.H.Hurter and Mabb., has been particularly well studied and used to treat a range of conditions, including its use as an aphrodisiac. Research on *V. nilotica* (L.) P.J.H.Hurter and Mabb. indicates that it possesses anti-inflammatory, antioxidant, antidiarrheal, antihypertensive, and antispasmodic properties, in addition to antibacterial, anthelmintic, anticancer, and acetylcholinesterase (AChE) inhibitory activities (Rather et al., 2015).

The **Poiretia** nodes consist of twelve endemic species to tropical regions of the Americas. Ethnobotanical reports highlight the use of *Poiretia* species for treating musculoskeletal ailments (Geck et al., 2016). However, some species, such as *Poiretia bahiana* C. Mueller, contain sabinene, a toxic monoterpene (Araújo et al., 2009). Moreover, *P. bahiana* C. Mueller also contains isoflavonoids with antifungal properties (Araújo et al., 2021). Another species, *Poiretia latifolia* Vogal, contains monoterpenes such as limonene, trans-dihydrocarvone, and carvone, which also exhibit antifungal activities (Nunes Alves Paim et al., 2018).

The **Indigofera** nodes are found in the genus *Indigofera*, one of the largest genera within the Fabaceae family (Schrire, 2013) and widely used for medicinal purposes (Gerometta et al., 2020). Several species have been employed as aphrodisiacs, including *Indigofera aspalathoides* Vahl ex DC. in India (Prabhu et al., 2014), *Indigofera cordifolia* B. Heyne ex Roth in Cameroon, Kenya, and Tanzania (Ajao et al., 2019), and *Indigofera flavicans* Baker in Botswana (Ajao et al., 2019). Additionally, *I. cordifolia* B. Heyne ex Roth has been used as an abortifacient in India (Jain et al., 2004) and *Indigofera sanguinea* N.E.Br. in Swaziland (Amusan et al., 2002). Phytochemical studies of various species in the genus have identified numerous

flavonoids and isoflavonoids, including apigenin, kaempferol, luteolin, quercetin, genistein, coumestrol, formononetin, and their derivatives (Gerometta et al., 2020).

Finally, the species from **Sesbania** nodes are found in tropical and subtropical regions worldwide (Govaerts, 2024). This genus has been used in traditional medicine for treating malaria (Budiarti et al., 2020), dermatology (Mutheeswaran et al., 2011), and headaches (Chellappandian et al., 2012). Phytochemical studies have shown that Sesbania species contain isoflavonoids (Hasan et al., 2012), though much of their potential pharmacological applications remain unexplored.

Despite the documented medicinal uses of many AF species in hot nodes, significant gaps remain in the phytochemical and pharmacological study, particularly regarding their potential estrogenic activities. The *Dialioideae* Legume Phylogeny Working Group subfamily, for instance, has shown promising preliminary results in identifying flavones in *A. leiocarpa* (Vogel) J.F.Macbr., yet its estrogenic potential remains untested. Similarly, while *D. regia* (Bojer ex Hook.) Raf. has been extensively studied, other species within the genus *Delonix* Raf. have not received the same attention. This lack of comprehensive research creates a valuable opportunity for further exploration, especially given the known pharmacological relevance of flavonoids. Investigating underexplored genera like *Poiretia* Sm., *Indigofera* L., and *Sesbania* Adams could yield novel estrogenic flavonoids and other bioactive compounds with potential therapeutic applications. As well as suggesting these lineages of the Fabaceae should be studied, we suggest that our methods could also be applied to other families which as less well known, and that this might increase the chances of identifying novel PEs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

KT: Conceptualization, Data curation, Formal Analysis, Methodology, Visualization, Writing – original draft, Writing – review and editing. JT: Methodology, Writing – review and editing. NV: Conceptualization, Methodology, Supervision, Writing – review and editing. JH: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review and editing.

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Conflict of interest

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1583365/full#supplementary-material

SUPPLEMENTARY DATA SHEET S1
The list of known PEs.

SUPPLEMENTARY DATA SHEET S2
Angiosperm species containing estrogenic flavonoids.

SUPPLEMENTARY DATA SHEET S3
The list of species of Fabaceae phylogeny containing estrogenic flavonoids.

SUPPLEMENTARY DATA SHEET S4
The list of species in hot nodes containing estrogenic flavonoids.

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