

Leveraging phytochemicals: the plant phylogeny predicts sources of novel antibacterial compounds



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ABSTRACT

The evolution and spread of antibiotic resistance have been the greatest threat to successful antibiotic treatment, and hence the driving force behind the search for new therapies. Ironically, none of our modern pharmaceutical antibiotics have been developed from plants, albeit plants have been used since antiquity in traditional medicine to fight bacterial infections. We phylogenetically analyzed 137 plant species with antibacterial activity and found plant families (Combretaceae, Cupressaceae, Fabaceae, Lamiaceae, Lauraceae, Myrtaceae, and Zingiberaceae) that are disproportionately important, with confamilials possessing phytochemicals exerting similar antibacterial mechanisms, as expected due to common ancestry. Phytochemicals produced were primarily involved in the disruption of the bacterial cell wall/membrane and inhibition of quorum sensing/biofilm production. The related families Combretaceae (white mangrove family) and Myrtaceae (guava family) were shown to inhibit quorum sensing, disrupting bacterial communication implicated in pathogenicity, due to their flavonoids. Cupressaceae (cypress family), though unrelated, also exhibited this antibacterial function. The unrelated families Fabaceae (bean family), Lamiaceae (mints), Lauraceae (laurel), and Zingiberaceae (ginger family) possessed phytochemicals, primarily essential oils, that affected bacterial cell membrane/cell wall integrity. Species in these various plant families may offer unique natural products that could be developed into new antibiotics. Our study reinforces the utility of the plant phylogeny in drug discovery.

INTRODUCTION

Though antibiotics have been proven effective in the treatment of many infections throughout history, infectious diseases remain a leading cause of death worldwide as a result of both emerging diseases and an increased prevalence of antibiotic resistant pathogens (Essack, 2001). A source of natural antibiotics may lie in medicinal plants, which have long been used traditionally to fight bacterial infections. Such plants are rich in a variety of secondary metabolites, including terpenoids, alkaloids, phenols, and flavonoids, which have been found to have antimicrobial properties in vitro. The microbial cell can be affected by plant secondary metabolites in different way including disruption of membrane function and structure, inhibition of DNA synthesis, protein inactivation, and inhibition of quorum sensing (Gupta & Birdi, 2017). Nonetheless, plant natural products have not yet been exploited as templates for pharmaceutical antibiotics. In this study, we phylogenetically analyzed plant species that have experimental evidence of antibacterial activity. The goal was to identify plant families with disproportionate importance as antibacterials, and if species within the same families (confamilial) shared a common antibacterial mechanism, as would be expected given the common ancestry. This study provides support to the utility of the plant phylogeny in identifying plant sources of novel antibiotics, and predicting pharmacological mechanisms for unexplored species, expediting our efforts in antibiotic drug discovery.

Scientific Name	Family	Antibacterial Mechanism	Accession Number
<i>Combretum spp</i>	Combretaceae	PN, EP, QS/BF	EU338166
<i>Terminalia chebula</i>	Combretaceae	CW/CM, QS/BF	FJ3818122
<i>Cupressus sempervirens</i>	Cupressaceae	QS/BF	L12571
<i>Juniperus drupacea</i>	Cupressaceae	QS/BF	HM024301
<i>Arachis hypogaea</i>	Fabaceae	CW/CM	KX257487
<i>Cajanus indicus</i>	Fabaceae	CW/CM	KU729879
<i>Perilla frutescens</i>	Lamiaceae	CW/CM, QS/BF	FJ513160
<i>Plectranthus amboinicus</i>	Lamiaceae	CW/CM, QS/BF	KX783974
<i>Laurus nobilis</i>	Lauraceae	CW/CM, QS/BF	HM850111
<i>Litsea cubeba</i>	Lauraceae	CW/CM	AY337734
<i>Swietenia mahogany</i>	Meliaceae	MU	FN599465

Table 1: A sample of the antibacterial plant species in this study. The antibacterial mechanisms of action for each species based on the literature are indicated (inhibition of BF: Biofilm; CM: Cell membrane; CW: Cell wall; EP: Efflux pump; PN: Protein and/or nucleic acid synthesis; QS: Quorum sensing; MU: Mechanism unknown), as well as their Genbank accession numbers corresponding to the DNA sequences used for phylogenetic reconstruction.

MATERIALS AND METHODS

137 plant species with antibacterial activity were compiled from PubMed. The plant phylogeny was reconstructed following methods in Guzman & Molina (2018). The antibacterial mechanisms of each plant species were determined based on literature and superimposed on the phylogeny using the Interactive Tree of Life (ITOL, Letunic & Bork, 2006), an online tool for the display and manipulation of phylogenetic trees. Families with three or more species, and majority of which shared a common antibacterial mechanism, were considered disproportionately represented on the phylogeny and potentially pharmacologically important for antibiotic drug discovery.

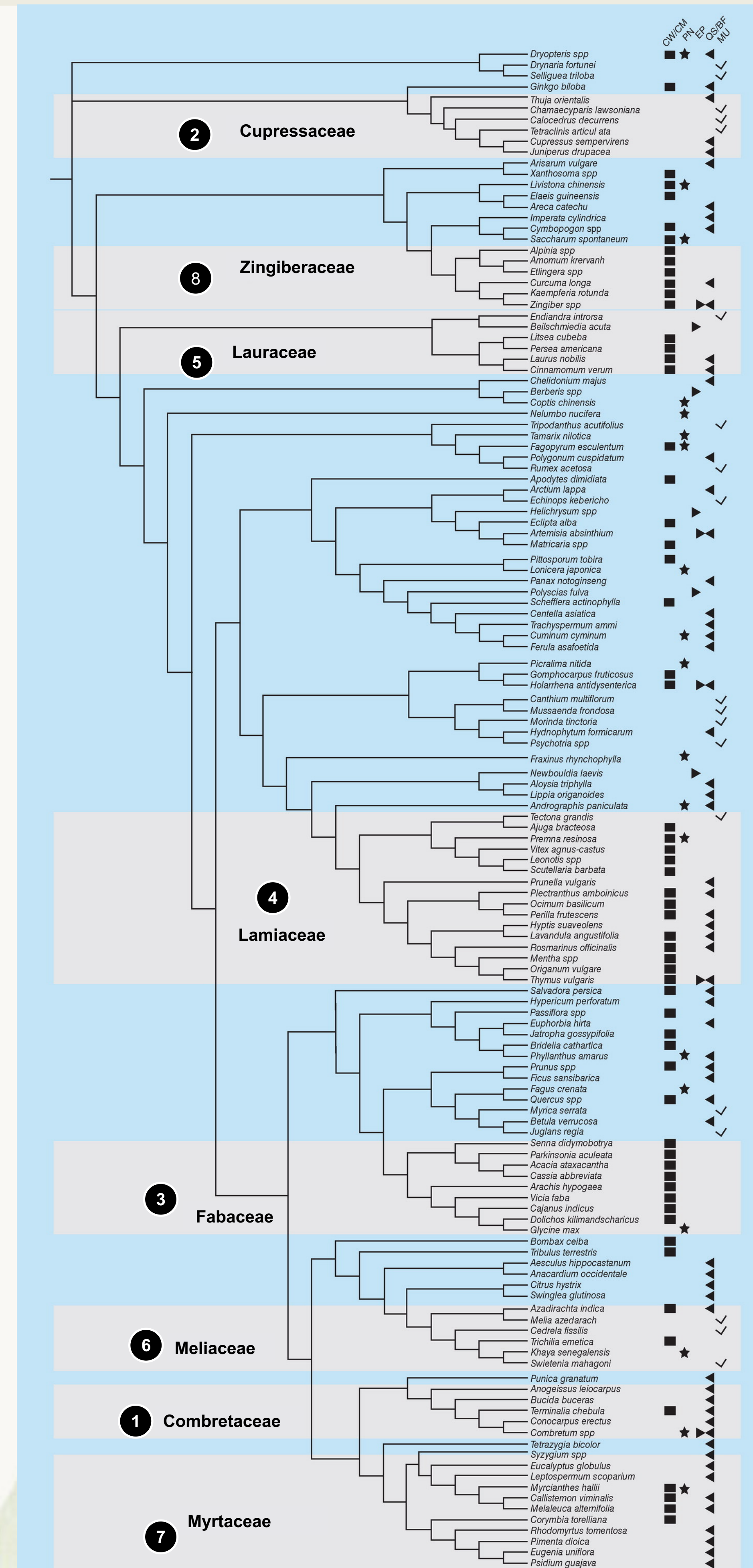


Figure 1: The phylogeny of plant species with antibacterial activity. Plant families having three or more species, where majority shared a common antibacterial mechanism (inhibition of BF: Biofilm; CM: Cell membrane; CW: Cell wall; EP: Efflux pump; PN: Protein and/or nucleic acid synthesis; QS: Quorum sensing; MU: Mechanism unknown). Numbers refer to families in summary table of antibacterial phytochemicals and photos of representative species to the right.

RESULTS AND DISCUSSION

Plant families with similar confamilial mechanisms of antibacterial activity were disproportionately represented on the phylogeny (see table below). Combretaceae, Cupressaceae, Lamiaceae, Lauraceae, Myrtaceae, Zingiberaceae, as well as Meliaceae, have disproportionate importance—at least 5% of their genera produce antibacterial compounds—though we were unable to find a precise mechanism of action for Meliaceae. Combretaceae, Cupressaceae and Myrtaceae possess phytochemicals that predominantly inhibit bacterial QS/BF. Lamiaceae, Lauraceae, Zingiberaceae have shown disruptive effects to bacterial CW and/or CM. Only 1% of Fabaceae are antibacterial, which is likely a result of the immense diversity of this family, though members of the family have consistently shown ability to damage CW. These plant families may indeed be potentially important sources of novel antibiotics with definite mechanisms of action. It is possible that this study underestimated the number of plant families and species that produce antibacterial agents, as it is likely that many have yet to be documented in the scientific literature. Nonetheless, our study provides a baseline understanding of plant taxa that produce antibacterial compounds and warrant further work in exploratory antibacterial screening.

These phylogenetic patterns in antibiotic pharmacology suggest that other unexplored species within these families may also possess similar phytochemistry and antibacterial effects. This study highlights the utility of the plant phylogeny in predicting novel sources of antibiotic drugs that may mitigate the pervasive problem of antibiotic resistance.

Family	Known mechanism of action	Primary active phytochemicals
1 Combretaceae	Quorum sensing/biofilm inhibitor	Flavonoids, e.g., catechin, naringenin; ellagic acid, ellagic acid derivatives, ellagitannins
2 Cupressaceae	Quorum sensing/biofilm inhibitor	Monoterpenes, e.g., limonene, α -pinene, δ -3-carene, α -terpinolene, camphor; sesquiterpenes, e.g., cedrol; polyphenols
3 Fabaceae	Inhibits cell wall and/or membrane	Phenolics, flavonoids
4 Lamiaceae	Inhibits cell wall and/or membrane	Terpenes/terpenoids, e.g., 1,8-cineole, pulegone, thymol, carvacrol, linalool, estragole, citral; carnosic acid; dihydroajugapitin; flavonoids, e.g., baicalin
5 Lauraceae	Inhibits cell wall and/or membrane	Aldehydes (e.g., cinnamaldehyde), aromatic alcohols (eugenol, benzyl alcohol); terpenoids (citral, citronellal, 1,8-cineole); endiandric acid and derivatives
6 Meliaceae	Mechanism unknown	Triterpenoid, e.g., limonoids
7 Myrtaceae	Quorum sensing/biofilm inhibitor	Monoterpenes, e.g., 1,8-cineole, α -pinene, α -terpineol; eugenol; flavonoids, e.g., quercetin
8 Zingiberaceae	Inhibits cell wall and/or membrane	Monoterpenes, e.g., 1,8-cineole, α -pinene, α -terpinene, β -pinene; flavonoids, e.g., isopanduratin A



REFERENCES

Poster adapted from Prasad MA, Zolnik C, Molina J. 2019. Leveraging phytochemicals: the plant phylogeny predicts sources of novel antibacterial compounds. Future Science OA doi: 10.2144/fsoa-2018-0124. <https://www.future-science.com/doi/10.2144/fsoa-2018-0124>