



The phylogeny predicts potential new sources of antibiotics from plants

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ABSTRACT

The evolution and spread of antibiotic resistance has been the greatest threat to successful antibiotic treatment, and hence the driving force behind the search for new therapies. 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 138 plant species with antibacterial activity and found 5 plant families that are disproportionately important, with confamilials exerting similar antibacterial mechanisms, as expected due to common ancestry. Myrtaceae (guava family) was shown to inhibit quorum sensing, disrupting bacterial communication implicated in pathogenicity, due to its flavonoids. The unrelated families Fabaceae (bean family), Lamiaceae (mints), Lauraceae (laurel), and Zingiberaceae (ginger family) possessed phytochemicals, mostly essential oils, that affected bacterial cell membrane integrity. Species in these 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 in vitro to have antimicrobial properties. 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 prods 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 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.

Family	Scientific Name	Common Name	Reference	Antibacterial Mechanism	Accession Number	Alternative Genbank Species
Acanthaceae	<i>Andrographis paniculata</i>	Green chiryta	(Banarjee et al., 2017; Shaikh et al., 2016; Tanwar et al., 2016)	Antimetabolite; Inhibits nucleic acid synthesis; Inhibits biofilm production	JQ933217	NA
Anacardiaceae	<i>Anacardium occidentale</i>	Cashew	(Madureira et al., 2011)	Inhibits/degrades cell wall	AY462008	NA
Apiaceae	<i>Centella asiatica</i>	Gotu kola	(Vasavi et al., 2016; Jose et al., 2017)	Inhibits quorum sensing; Inhibits biofilm production	D44559	NA

Table 1: A sample of the 138 antibacterial plant species in this study. The antibacterial mechanisms of action for each species based on the reference are indicated, as well as their Genbank accession numbers corresponding to the DNA sequences used for phylogenetic reconstruction.

MATERIALS AND METHODS

138 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.

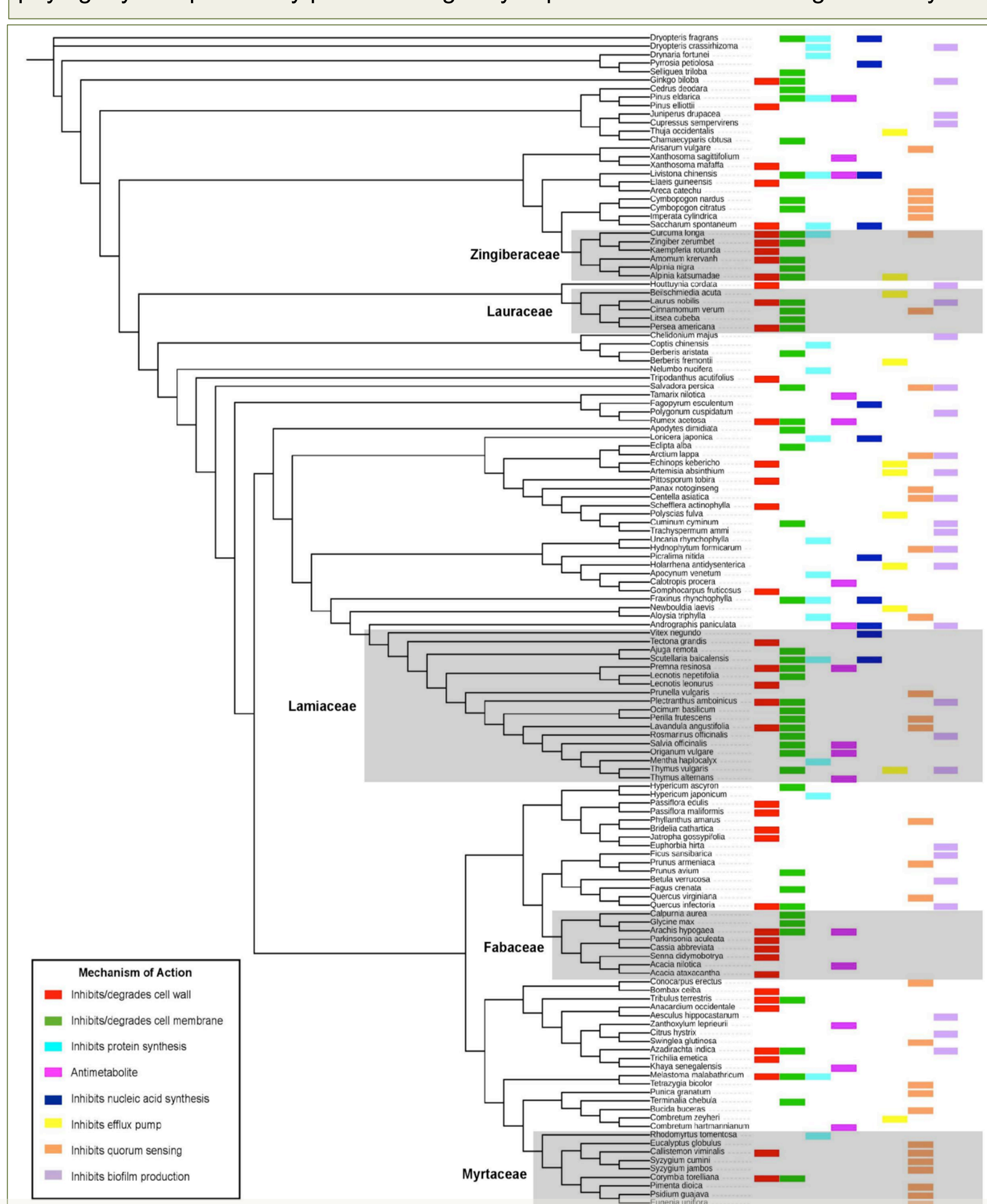
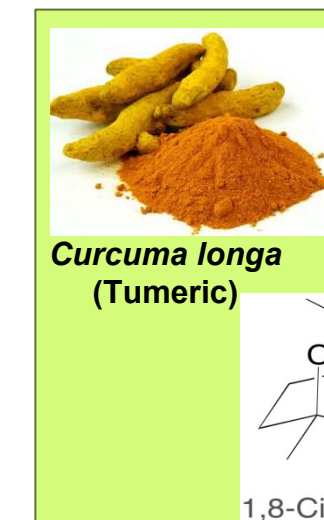


Figure 1: The phylogeny of plant species with antibacterial activity. Plant families having three or more species, where majority shared a common antibacterial mechanism, are labeled and shaded.

RESULTS AND DISCUSSION

Phylogenetic analysis revealed five plant families that are over-represented in the plant phylogeny (Fig. 1). Myrtaceae (guava family) was shown to inhibit quorum sensing, disrupting bacterial communication implicated in pathogenicity, due to its flavonoids. The unrelated families Fabaceae (bean family), Lamiaceae (mints), Lauraceae (laurel), and Zingiberaceae (ginger family) possessed phytochemicals, mostly essential oils, that affected bacterial cell membrane integrity, consequently causing cell lysis.



Zingiberaceae (ginger family) natural products affect bacterial cell membrane and cell wall. Essential oil constituents (e.g. phenols, terpenes) exert antibacterial activities via permeabilization of bacterial membranes (Tripathi et al., 2013). The monoterpene 1,8-cineole and phenolic compounds have been reported in the antibacterial extracts of turmeric *C. longa* and cardamom *Amomum krervanh*.



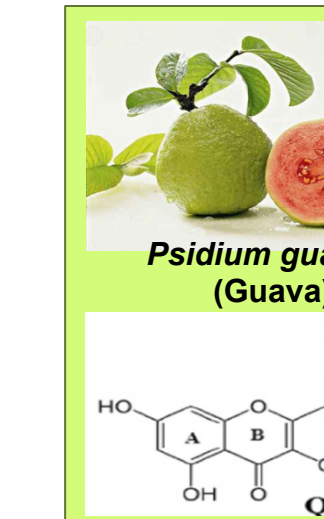
Lauraceae (bay leaf family) natural products disrupt bacterial cell membranes. Members of Lauraceae possess essential oil components (e.g. 1,8-cineole, sabinene, carvacrol, linalool, terpineol) that disintegrate the lipopolysaccharide layer of Gram(-) bacteria (Li et al. 2014; Sahin & Candan, 2013; Ramos et al., 2011).



Lamiaceae (mint fam) phytochemicals disrupt bacterial cell membranes. Lamiaceae essential oils such as those found in lavender, basil, thyme and oregano (e.g. linalool, thymol, carvacrol) can lyse cell membranes (Al-Mariri & Safi, 2013).



Fabaceae (bean family) phytochemicals destroy the bacterial cell wall A variety of active constituents, such as tannins, flavonoids, alkaloids, and terpenes are found in members of this family (Molares et al., 2011). The emergence of Fabaceae here as phylogenetically important may be an artifact of its immense species diversity, hence, easy accessibility. Despite the lack of a definite phylogenetic phytochemical pattern, this family is rife with antibacterial secondary metabolites that can be pharmacologically exploited.



Myrtaceae (guava family) flavonoids disrupt bacterial cell communication (quorum sensing, QS). Majority of species in the family inhibited QS implicated in pathogenicity. Flavonoids in Myrtaceae such as quercetin and quercetin-3-O-araboside have been found to suppress virulence via allosteric inhibition of quorum sensing receptors. (Paczkowski et al., 2017).

CONCLUSION

Phylogenetic reconstruction of plant species with antibacterial activity has revealed 5 important plant families that may be pharmacologically relevant for antibiotic drug discovery. Associations between phytochemistry and antibacterial effects were evident, with the flavonoid-rich Myrtaceae inhibiting quorum sensing, while the terpenoids and phenolic compounds in the unrelated families of Zingiberaceae, Lauraceae, Fabaceae, and Lamiaceae were implicated in cell membrane/cell wall permeabilization and lysis. 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 potential new sources of antibiotic drugs that may mitigate the pervasive problem of antibiotic resistance.

BIBLIOGRAPHY

Poster adapted from Prasad, M.A. (Spring 2018). "Phylogenetic analysis of plants with antibacterial activity reveals certain plant families relevant for antibiotic drug discovery". MSc thesis under the supervision of Dr. J. Molina (all literature citations found therein), Long Island University, pp. 1-57.