THE UNTAPPED POTENTIAL OF MEDICINAL PLANTS FOR TACKLING AMR

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Quave Research Group
MEDICAL ETHNOBOTANY AND ANTI-INFECTIVE DRUG DISCOVERY
Many Essential Medicines were Discovered in Plants

CANCER
- Hyoscine
- Hyoscine butylbromide
- Atropine
- Quinine
- Dihydroartemisinin
- Artemether
- Artesunate

HEART DISEASE
- Codeine
- Acetylsalicylic acid
- Morphine
- Nicotinamide
- Warfarin
- Paclitaxel
- Vinblastine
- Vinorelbine

INFECTION
- Ephedrine
- Valproic acid
- Digoxin
- Folic acid
- Caffeine citrate
- Etoposide
- Ascorbic acid

PAIN
- Metformin
- Salicylic acid

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Plants are Key to Healthcare Across the Globe

Medicinal plants constitute the primary pharmacopoeia for 70-95% of people living in most developing countries. Habitat loss, overharvesting, and climate change threaten access to medicinal plants for health.
What do we know about plant-derived antibiotics?

- 958 plant species
- We report details on 70 medicinal plants from the 15 most studied plant families

Phylogenetic distribution strongly supports the chemical evolution across plant clades, especially in more derived eudicot families.

A Phylogenetic Perspective

- Antibiotic activity found in plant extracts from 51 of 79 vascular plant orders throughout the phylogenetic tree
  - Mainly in eudicots
  - Asterids mainly represented
- Most studied families with activity:
  - Asteraceae
  - Fabaceae
  - Lamiaceae

A Chemical Perspective

- 459 plant-derived compounds with MICs < 100 µg/mL reviewed
- Chemical data deposited with Pew Charitable Trusts SPARK platform for antibiotic drug discovery (data also available in spreadsheet form with SMILES in supporting info)

Porras, Chassagne, et al. (2021) Ethnobotany and the Role of Plant Natural Products in Antibiotic Discovery. Chemical Reviews 121, 6, 3495–3560
Alkaloids

A

![Pie chart showing distribution of alkaloids]

- Isoquinolines, Aporphines, and Phenanthrenes
- Indoles
- Piperidines
- Quinolines
- Other Alkaloid Derivatives

Total: 26

B

![Bar chart showing number of compounds in different families]

- Rubiaceae
- Papaveraceae
- Cucurbitaceae
- Buxaceae
- Apocynaceae
- Ranunculaceae
- Annonaceae
- Juncaceae
- Rutaceae
- Asteraceae

Number of Compounds

Isoquinolines, Aporphines, and Phenanthrenes

<table>
<thead>
<tr>
<th>Species</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Listeria monocytophages</em></td>
<td>2.5</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>2.5</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>5</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae (ESBL-KP)</em></td>
<td>10</td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
<td>10</td>
</tr>
<tr>
<td><em>Bacillus cereus</em></td>
<td>1.25</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>1.25</td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
<td>1.25</td>
</tr>
<tr>
<td><em>Staphylococcus sp. (ORCN5)</em></td>
<td>1.25</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>2.5</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae (ESBL-KP)</em></td>
<td>2.5</td>
</tr>
</tbody>
</table>
Path from Ethnobotanical Knowledge to Compound Discovery

- Antibiotics
- Antibiotic resensitizing adjuvants
- Anti-virulence therapies
  - Toxins
  - Biofilms

**Steps in the Process:**

1. Ethnobotanical information
2. Preparation of extracts
3. Bioassay-guided fractionation
4. Medicinal chemistry, SAR
5. Clinical studies
6. Toxicology, Pharmacology, ADME, PK/PD, Formulation
7. DRUG
3-oxo-olean-12-en-28-oic acid (1), oleanonic acid 3-oxo-lanosta-7,24-dien-26-oic acid (2) (Z)-masticadienoic acid (Z)-schinol (3)

Tang et al. (2020) Triterpenoid acids isolated from *Schinus terebinthifolia* fruits reduce *Staphylococcus aureus* virulence and abate dermonecrosis. Scientific Reports 10, 8046.
1st Report of Triterpenoid Acids with Potent Anti-virulence Effects against S. aureus

Tang et al. (2020) Scientific Reports
Clerodane Diterpene Resensitizes MRSA to β-Lactams

Dettweiler et al. (2020) A clerodane diterpene from Callicarpa americana resensitizes methicillin-resistant Staphylococcus aureus to β-Lactam antibiotics. ACS Infectious Diseases. 6, 1667-1673.