Different Herbal Products -Ameliorates B-Lactamase Inhibition

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Abstract: Beta-lactamase is an enzyme formed by medically important Gram-positive and Gram-negative bacteria, and is in charge for their resistance to β-lactam antibiotics. Most commonly herbal products are used to inhibit activity of bacteria producing β-lactamase.


INTRODUCTION

1. Herbal products

• Botanical drugs: a future for herbal medicines
  In recent years, herbal medicines have attracted strong attention in the United States and worldwide, as part of a larger fascination with natural products. This explores the future of herbal medicines in the United States and makes the case that botanical drug, as a new drug model for herbal medicines, will lend a much-needed arsenal to the perennial fight against human diseases. Due to an unfavorable regulatory climate, few US companies engage in developing drug products from herbal medicines. [1]

• Global promotion of herbal medicine: India’s opportunity
  Due to side effects of synthetic products, herbal products are gaining popularity in the world market. In spite of well-practiced knowledge of herbal medicine and occurrence of a large number of medicinal plants, the share of India in the global market is not up to the mark. India is also one of the twelve Meg for the prevention and cure of different human diseases. [2]

• Recent approaches in herbal drug standardization
  The quality control standards of various medicinal plants used in indigenous system of medicine are becoming more relevant today in view of commercialization of formulations based on medicinal plants. For standardization and quality assurance purposes, following three attributes are desirable: i) Authenticity, ii) Purity and iii) Assay. [3]

2. β-Lactamase

• β-Lactamase is a group of enzymes capable of hydrolyzing the amide bond in the β-lactam ring of β-lactam antibiotics such as carbapenems, penicillin and cephalosporin, and monobactam. Beta-lactam antibiotics structurally consist of a thiazolidine ring connected to a beta-lactam ring, which is attached to a side chain. [9]

• Beta-lactam constitutes one of the most important antibiotics families in worldwide use. More than fifty products were developed, exhibiting sometimes expanded spectra of action, low toxicity and in many cases, reasonable cost. Resistance to this antibiotic family can be attributed to several factors. However, the production of beta-lactamases (EC 3.5.2.6) is the major determinant of resistance. These enzymes which hydrolyse the beta-lactam ring have been the subject of extensive microbiological, biochemical and genetic investigations. More than 500 beta-lactamases have been and divided into four molecular classes: A, B, C and D. The majority of these enzymes have been described in Gram negative bacteria which are responsible for numerous infectious diseases and are generally multidrug resistant. [6]

Figure 1: Protection of penicillin-susceptible bacteria from penicillin by beta-lactamase -producing bacteria. [15]

• Beta-lactamase-producing bacteria (BLPB) can play an important role in polymicrobial infections. They can have a direct pathogenic impact in causing the infection as well as an indirect effect through their ability to produce the enzyme beta-lactamase. [13]

• The two families of β-Lactamase include “Metallo-β-Lactamase” and “Serine-β-Lactamase”. [9] The metallo- and serine beta-lactamases in the cell extracts were distinguished on isoelectric focusing (IEF) gels by using the following procedures. (i) Cell
lysates were pre-incubated with 83mM EDTA prior to IEF and subsequent visualization with nitrocefin, and (ii) after IEF, the gels were overlaid with either 1 mM zinc sulfate or 100microM BRL 42715 before staining with nitrocefin. Bands of beta-lactamase activity which were removed by BRL 42715 but unaffected by EDTA or zinc sulfate were categorized as **serine beta-lactamases**. Bands which were unaffected by BRL 42715 but inhibited by EDTA or enhanced by zinc sulfate were classified as **metallo-beta-lactamases**.\\(^{[14]}\\)

3. **Why we should use herbal drugs instead of synthetic?**

The indiscriminate use of synthetic anti-microbial drugs commonly used in the treatment of infectious diseases has also led to the development of multiple drug-resistant strains of bacteria over the years. In addition to this problem, adverse effects on the host including hypersensitivity, immunosuppressant, and gastrointestinal upset and allergic reactions are sometimes attributed to the use of these anti-microbial drugs. This has drawn the attention of the scientific community to biologically active compounds derived from medicinal plants since they present less desirable side effects. More than half of all modern clinical drugs are **plant-derived**. This shows that plant products play a significant role in the development of drugs by the pharmaceutical industry. The consumption of plant materials contribute immensely to the improvement of human health and nutrition.\\(^{[11]}\\)

Several plant extracts have exhibited synergistic activity against microorganisms. The observed synergy and mechanism of action between natural products including flavonoids and essential oils and synthetic drugs in effectively combating bacterial, fungal and mycobacterial infections. Mode of action of combination differs significantly than that of the same drugs acting individually; hence isolating a single component may lose its importance thereby simplifying the task of pharma industries.\\(^{[16]}\\)

**EFFECTS OF HERBAL PRODUCTS ON β-LACTAMASE INHIBITION**

Antimicrobial resistance problem has forced to switch over to the use of plant herbs for various infectious conditions.\\(^{[5]}\\) In the study, β-Lactamase inhibitor activity was analyzed by Iodometry and Bioassay methods. **Sulbactum** was used as the standard β-Lactamase enzyme inhibitor throughout the study. In the current study, the β-Lactamase inhibitor activity of 68 extracts from Indian herbs and spices was surveyed. Most promising results of the β-Lactamase inhibitor activity in vivo and in vitro were achieved from the herbal extracts of **Baheda** (Terminaliabellerica), **Ginger** (Zingiberofficinale), **Brahmi** (Bacopamonnieri), **Garlic** (Allium sativum), **Gurmar** (Gymnemasylvestre), **Satavar** (Asparagus racemosus) and **Pomegranate** (Punicagranatum) peels and seeds.
against Staphylococcus as the test organism. As many microorganisms are becoming resistant to antibiotics, it is indeed necessary to find new β-Lactamase inhibitors. [6]

In efforts to find new active β-Lactamase inhibitors, this study investigated 16 Cameroonian plants belonging to 10 families which were evaluated for anti-β-Lactamase activity. The investigation showed that extracts 2, 6, 3 and 5 of the 16 plants investigated presented interesting in vitro β-Lactamase inhibition (over 90%), respectively, of the β-lactamas TEM-1, OXA-10, IMP-1 and P99. These extracts were from Mammee africana (all β-lactamas), Garcinia lucida, G. kola (OXA-10, IMP-1 and P99), Brideliamicrantha (OXA-10, P99), Occhnazefili (OXA-10, P99), Prunusafrcicana (IMP-1) and Adenialobata (TEM-1). After elimination of tannins (according to the European Pharmacopoeia) the extracts from B. micrantha, G. lucida and M. africana were tested further for their anti-β-Lactamase activity. The extracts from B. micrantha and G. lucida exhibited potent inhibitory activity, respectively, of β-Lactamase OXA10 (IC50 = 0.02 mg/mL) and P99 (IC50 = 0.01 mg/mL). The anti-β-Lactamase activity of M. africana extract was weak. The isolation and the structural elucidation of the active constituents of G. lucida and B. micrantha will provide useful leads in the development of β-Lactamase inhibitor. [10]

The crude plant extracts demonstrated broad spectrum antibacterial activity against all bacteria tested with inhibition zones in the range of 8-30 mm. The minimal inhibitory concentration (MIC) values of different plant extracts against the tested bacteria were found to range from ≤ 0.3 to ≥ 10 mg ml⁻¹. The most active plant extracts were from Dorteniapicta and Brideliamicrantha (MIC: 1.25-10 mg ml⁻¹) on beta-lactam-resistant Gram-negative bacilli and the extracts from B. micrantha, Mallotuspossitifolius, Garcinia lucida, Garcinia. Kola, Campylperspermum densiflorum (leaves) and C. zenkeri (root) on beta-lactam-resistant Gram-positive cocci (MIC: ≤ 0.3-5 mg ml⁻¹). The stem bark of B. micrantha and the leaves of D. picta were most active towards beta-Lactamase producing Gram-negative bacilli. This study shows that medicinal plants could be sources of compounds which can be used to fight against beta-lactam resistant bacteria. [4]

Table 1: Details on the medicinal plant species that were investigated [4]

<table>
<thead>
<tr>
<th>Family</th>
<th>Botanical name</th>
<th>Site of collection</th>
<th>Part used</th>
<th>Uses in traditional medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apocynaceae</td>
<td>Picralimanitida(Stapf.) T&amp;H.Durand</td>
<td>Mbalayo (Centre)</td>
<td>Seed, leaves, roots</td>
<td>Hypertensionfever, malaria, anti-inflammatory, antimicrobial</td>
</tr>
<tr>
<td>Clusiaseae</td>
<td>Garcinia lucida Vesque G. kola Heckel</td>
<td>Lolodorf (Sud)</td>
<td>Seed</td>
<td>Gastric ulcer, fermentation of palm wine, gynecological infections, gastro-intestinal infections.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NgokMapubi (Centre)</td>
<td>Stem bark</td>
<td></td>
</tr>
<tr>
<td>Moraceae</td>
<td>Dorsteniapicta Bur.</td>
<td>Tombel (South west)</td>
<td>Leaves</td>
<td>Diarrhoea, infected wounds, antiinflammatory, antimicrobial, eye diseases,</td>
</tr>
<tr>
<td>Rosaceae</td>
<td>Prunus africana (Hook. F.) Kalkman</td>
<td>Balembo (West)</td>
<td>Leaves</td>
<td>Dermatological infection, abdominal pain, purgative, snake bites</td>
</tr>
</tbody>
</table>

Ethanoic extracts and some fractions from 10 Indian medicinal plants, known for antibacterial activity, were investigated for their ability to inhibit clinical isolates of β-Lactamase producing meticillin-resistant Staphylococcaus aureus (MRSA) and meticillin-sensitive S. aureus (MSSA). Synergistic interaction of plant extracts with certain antibiotics was also evaluated. The MRSA test strains were found to be multi-drug resistant and also exhibited high level of resistance to common β-lactam antibiotics. These strains produced β-lactamas, which hydrolyze one or other β-lactam antibiotics, tested. The extract of the plants from Camellia sinensis (leaves), Delonixregia (flowers), Holarrhenaaantidysenteria (bark), Lawsoniainerms (leaves), Punicagranatum (rind), Terminaliachebula (fruits) and Terminaliabelerica (fruits) showed a broad-spectrum of antibacterial activity with an inhibition zone size of 11 mm to 27 mm, against all the test bacteria. The extracts from the leaves of Ocimum sanctum showed better activity against the three MRSA strains. The antibacterial potency of crude extracts was determined in terms of MIC by the tube dilution method. MIC values, of the plant extracts, ranged from 1.3 to 8.2 mg/ml against the test bacteria. Further, the extracts from Punicagranatum and Delonixregia were fractionated in benzene, acetone and methanol. Antibacterial activity was observed in acetone as well as in the methanol fractions. In vitro synergistic interaction of crude extracts from Camellia sinensis, Lawsoniainerms, Punicagranatum, Terminaliachebula and Terminaliabelerica was detected with tetracycline. Moreover, the extract from Camellia sinensis also showed synergism with ampicillin. [8]

Plants produce several secondary metabolites for their survival in adverse environments. Several phytoconstituents have antimicrobial properties and have been used in traditional medicine for a long time. Virtual screening, molecular docking, and dynamic simulation methods are followed to get the best inhibitor for L1 β-lactamase. Finally, four compounds are selected to set

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for molecular dynamics simulation. After all the computational calculations, withanolideR is found to have a better binding and forms a stable complex with the protein. This compound can act as a potent natural inhibitor for L1 β-lactamase.\(^9\)

Antibacterial activities of essential oils (Eos) from different Iranian medicinal plants against TEM gene positive ESBL-producing E. coli strains isolated from urine samples of patients with urinary tract infections. Eos were extracted using hydro-distillation method. ESBL-producing E. coli strains were isolated from urine samples of patients with urinary tract infections. Then, ESBL-producing strains were identified using double disk synergy test, phenotypic disc confirmatory test and polymerase chain reaction (PCR) for TEM gene detection. The antibacterial activity of the Eos from different plants (Achilleawilhelmsii C. Koch, Echinophoraplatyloba DC, Lallemantiaroyleana, NepetapersicaBoiss, Pulicaria vulgaris Gaertn, Salvia nemorosa, and SaturejaintermediaC.A.Mey) and antibiotics against ESBL-producing strains was studied using the microdilution method for the evaluation of the minimum inhibitory concentration (MIC). The 103 out of 295 E. coli strains with 97 (90.65%) TEM gene distributions were identified as ESBL-producing strains. All of the Eos derived from different plants displayed high inhibitory effects against ESBL-producing E. coli strains.\(^11\)

Ethanol extracts of 100 traditional Chinese medicines for beta-lactamase inhibitors activity was screened and assayed by using enzyme assay colorimetric KMmethod (Ziachang et al., 2009). Inhibitory potential of Ocimum sanctum, Punicagranatum, Syzygiumaromaticum, Glycyrrhizaglabra, Piper longum, Zingiberofficinalis and fifteen other plant extracts against extended spectrum beta lactamase enzyme using chromogenic substrate CENTA was also reported (Solanki and Selvanayagam, 2013).\(^15\)

Acetone extracts of ten medicinal plants at various concentrations (100 -500 µg ml\(^{-1}\)) were used to estimate their inhibitory effect on β-lactamase activity by the invitro-iodometry method (spectrophotometrically). The results exhibited that the β-lactamase activity of both S. scuri and K. pneumoniae was inhibited by acetone extracts of ten medicinal plants.\(^18\)

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