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 herbals products are used to inhibit activity of bacteria producing β-lactamase.

Keyword: β-Lactamase inhibitor, Herbal Product, Extracts, Antimicrobial resistance.

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. Thisexplores 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 desirablei) 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]

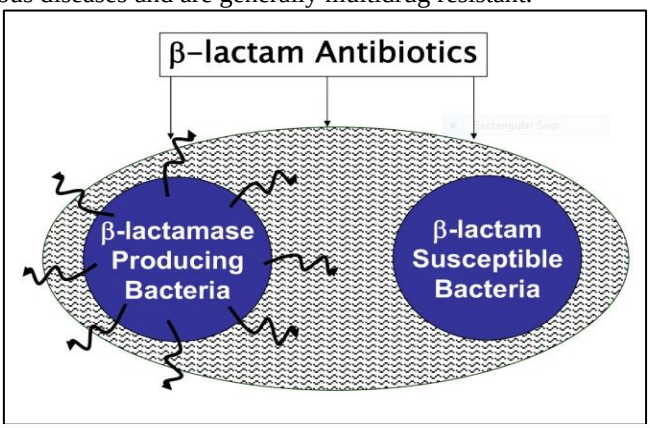

Figure 1:Protection of penicillin-susceptible bacteria from penicillin by beta-lactamase -producing bacteria.[15]

- 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.[15]
- The two families of β-Lactamase include “Metallo-β-Lactamase” and “Serine-β-Lactamase”.[9]Themetallo- 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]

Metallo beta lactamase

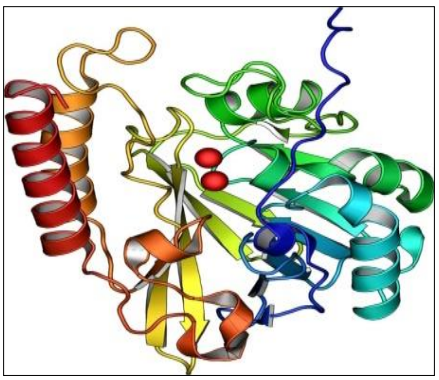

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Figure 2: Metallo-beta-Lactamase L1 from Stenotrophomonasmaltophilia protein[9]

Serine beta lactamase

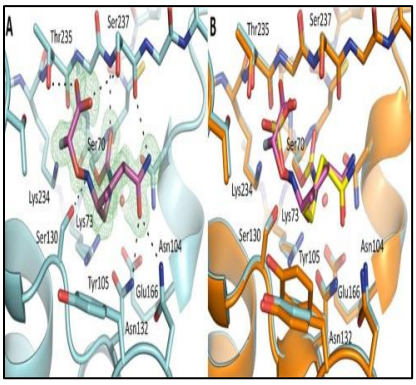

Figure 3:ETX1317 acyl enzyme complex with CTX -M-14 β-Lactamase. [13]

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 effectson 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 materialscontribute immensely to the improvement of human health and nutrition.[11]

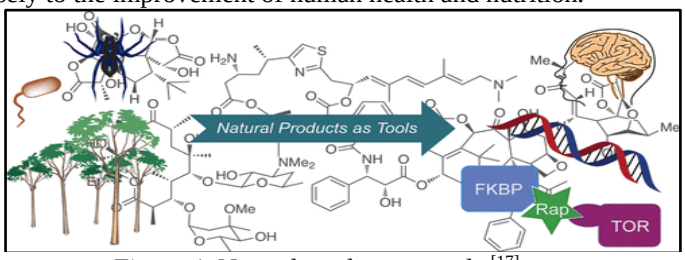

Figure 4: Natural products as tools [17]

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

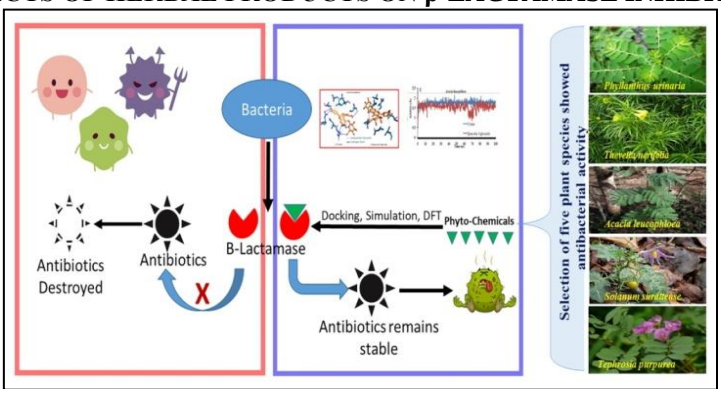

Figure 5: Selection of five plant species showed antibacterial activity.[12]

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 bioactive 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-lactamases **TEM-1, OXA-10, IMP-1 and P99**. These extracts were from **Mammeaafricana** (all β-lactamases), **Garcinialucida**, G. kola (OXA-10, IMP-1 and P99), **Brideliamicrantha** (OXA-10, P99), **Ochnaafzelii** (OXA-10, P99**), Prunusafricana** (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 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, **Mallotusoppositifolius**, Garcinialucida, Garcinia. Kola, **Campylospermumdensiflorum** (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]

Family	Botanical name	Site of collection	Part used	Uses in traditional medicine
Apocynaceae	*Picralimanitida*(Stapf.) T&H.Durand	Mbalmayo (Centre)	Seed, leaves,roots	Hypertensionfever, malaria,anti-inflammatory,antimicrobial
Clusiaseae	*GarcinialucidaVesque* *G. kola* Heckel	Lolodorf (Sud) NgokMapubi (Centre)	Seed Stem bark	Gastric ulcer, fermentation of palm wine, gynecological infections, gastro-intestinal infections.
Moraceae	*Dorsteniapicta*Bur.	Tombel (South west)	Leaves	Diarrhoea, infected wounds, antiinflammatory, antimicrobial, eye diseases,
Rosaceae	*Prunusafricanus* (Hook. F.) Kalkman	Balembo (West)	Leaves	Dermatological infection, abdominal pain, purgative, snake bites

Ethanolic 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 **methicillin-resistantStaphylococcusaureus(MRSA)**and **methicillin-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-lactamases, which hydrolyze one or other β-lactam antibiotics, tested. The extract of the plants from **Camellia sinensis**(leaves),**Delonixregia**(flowers),**Holarrhenaantidysenteria**(bark),**Lawsoniainermis** (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 ofMICby 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, Lawsoniainermis, 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

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.[7]

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).[5]

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 thatthe β-lactamase activity of both S.sciuri and K.pneumoniae was inhibited by acetone extracts of ten medicinal plants. [18]

REFERENCES

1. Weishi Li J. Contemp. Health L. &Pol'y 19, 117, 2002
2. NK Dubey, Rajesh Kumar, PramilaTripathiCurrent science 86 (1), 37-41, 2004
3. NP Yadav, VK Dixit Int J IntegrBiol 2 (3), 195-203, 2008.
4. The in-vitro antimicrobial activity of some traditionally used medicinal plants against beta-lactam-resistant bacteria. Joseph Gangoué-Piéboji1,2, Noelly Eze3, Arnaud Ngongang Djintchui4, Bathélémy Ngameni5, Nolé Tsabang1, Dieudonné E. Pegnyemb4, Lucie Biyiti1, Pierre Ngassam3, Sinata Koulla-Shiro6 and Moreno Galleni2.
5. Inhibitory effect of herbs on extended spectrum beta lactamase enzyme from Escherichia coli of healthy broilersArpitaShrivastav, R.K. Sharma, Neeraj Shrivastav1, VidhiGautam, S.K. Jain.
6. Sohail S, Rajiv L, Praneeta K, Tandon GD. Beta lactamase inhibitors from indigenous herbs and spices. Res J Pharm BiolChem Sci. 2014;5 (2):275-85.
7. Antibacterial activities of essential oils from Iranian medicinal plants on extended-spectrum Î²- lactamase-producing Escherichia coli J Sharifi-Rad, D Mnayer, A Roointan, F Shahri, SAM Ayatollahi, M Sharifi-Rad, N Molaee Cellular and molecular biology 62 (9), 75-82, 2016.
8. Effect of certain bioactive plant extracts on clinical isolates of β-lactamase producing methicillin resistant Staphylococcus aureusFarrukhAqil, M SajjadA Khan, MohdOwais, Iqbal Ahmad Journal of Basic Microbiology: An International Journal on Biochemistry, Physiology, Genetics, Morphology, and Ecology of Microorganisms 45 (2), 106-114, 2005.
9. Identification of natural inhibitor against L1 β-lactamase presents in StenotrophomonasmaltophiliaDhananjay Jade, Michael A Harrison, ShobanaSugumar Journal of Molecular Modeling 28 (11), 1-14, 2022.
10. Screening of some medicinal plants from cameroon for *β*-Lactamase inhibitory activityJosephGangoué-Piéboji,StéphaneBaurin,Jean-Marie Frère,PierreNgassam,BathelemyNgameni,AnatoleAzebaze,DieudonnéEmmanuelPegnyemb,JeanWatchueng,ColetteGoffin,MorenoGallen.
11. Leaf Extracts of Vernoniaamygdalina Del. from Northern Ghana Contain Bioactive Agents that Inhibit the Growth of Some Beta-lactamase Producing Bacteria in vitroOseni Lateef Adebayo1, Abugri James1, SumabeBalagra Kasim1 and Onilimor Peter Jagri1 1Department of Applied chemistry & Biochemistry, University for Development Studies, P.O. Box 24, Navrongo, Ghana.
12. Insight into the screening of potential beta-lactamase inhibitors as anti-bacterial chemical agents through pharmacoinformaticsstudyPratapParida, ShovonlalBhowmick, AchintyaSaha&MdAtaul Islam
13. Discovery of an Orally Available Diazabicyclooctane Inhibitor (ETX0282) of Class A, C, and D Serine β-LactamasesThomas F. Durand-Réville, Janelle Comita-Prevoir , Jing Zhang , Xiaoyun Wu ,Tricia L. May-Dracka, Jan Antoinette C. Romero, Frank Wu , April Chen, Adam B. Shapiro, Nicole M. Carter, Sarah M. McLeod, Robert A. Giacobbe, Jeroen C. Verheijen, Sushmita D. Lahiri, Michael D. Sacco, Yu Chen, John P. O'Donnell, Alita A. Miller, John P. Muellerand Rubén A. Tommasi.
14. Rapid identification of metallo- and serine beta-lactamases Authors: D J Payne, R Cramp, J H Bateson, J Neale, D Knowles
15. The role of beta-lactamase-producing-bacteria in mixed infections ItzhakBroo.
16. Synergism between natural products and antibiotics against infectious diseasesAuthor links open overlaypanelShanmugamHemaiswarya[a]AnilKumarKruthiventi[b]MukeshDle[a]
17. Natural Products as Chemical ProbesErin E. Carlson.
18. Research Journal of Pharmaceutical, Biological and Chemical Sciences Beta-Lactamase Inhibitory Effect of Some Medicinal Plants. Huda S A Al-Hayanni1, and Hamed M El-Shora2.