

Holistic Herbs - A Natural Arsenal for Contention between Bugs and Drugs

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Editorial

Nosocomial infections are one of the major causes of disease globally, leading to the most frequent adverse events in healthcare setups worldwide [1]. Millions of patients are affected by nosocomial infections each year globally, bringing about significant mortality and economic losses in healthcare systems. At any given time, the prevalence of health care-associated infections in developed countries varies between 3% to 15% [2]. Moreover, nosocomial infections are becoming even more complicated to treat as antibiotic resistance surfaces up. Recent reports from Centre for Disease Control (CDC) and World Health Organization (WHO) have indicated that nosocomial infections accounts for approximately 2 million infections and 90,000 deaths per year, out of which nearly 23% deaths are attributed to re-emerging antibiotic resistant pathogens [3]. Antibiotics comprising bactericidal or bacteriostatic chemotherapeutic agents are

presently the only available therapeutic option for the management and deterrence of infectious diseases. However, several drug resistant microbes are emerging as a result of continuous mutations, thereby restraining the efficacy of such pharmaceuticals [4]. Over use of antibiotics imposes selective pressure on a specific population of bacteria, thereby allowing the resistant bacteria to thrive and the susceptible bacteria to die off [5].

Eventually, the re-emergence of classical pathogens as mutated species of higher virulence is a major threat. One recent example of newly emerging multi-drug resistant pathogens is the ESKAPE category of microorganisms, as designated by CDC. ESKAPE pathogens, i.e., *Enterobacter species*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Proteus vulgaris* and *Enterococcus faecium* are referred to as microorganisms that are capable of 'escaping' the biocidal action of antibiotics and collectively representing new

paradigms in pathogenesis, transmission and resistance. These are responsible for 30-50% of nosocomial infections in the healthcare establishments [6].

These multi-drug resistant (MDR) pathogens have become customary in healthcare institutions, often resulting in treatment failure, and posing a serious threat to acutely ill patients, thereby becoming a broader problem for both healthcare institutions as well as community [7]. ESKAPE pathogens are although multi-drug resistant but they show some sensitivity towards IIIrd line antibiotics including Tigecycline, Colistin, Aztreonam and Polymyxin. However, these antibiotics are often associated with adverse drug reactions and complications such as hepato-renal toxicity [8]. Several new alternative peptides are also under clinical studies to be proven as an effective treatment methodology for MDR strains, *e.g.*, GSK 299423 targeting reproduction of multi-drug resistant bacteria [9]. However, the cost of these antimicrobial peptides will still remain a decisive factor restricting its extensive usage. In order to develop proper and effective control strategies, drugs and devices against such dreadful microorganisms, the need of the hour is to promptly develop alternative therapies by synergistically using synthetic and herbal drugs.

Medicinal herbs, as potential source of new chemical entities, have attained a significant role in health care system all over the world for both humans and animals. It effectively mitigates a diseased condition as well as serves as a potential material for maintaining proper health. The ability of natural plant products to serve as a source of antimicrobial leads/ agents, have been continually and extensively studied owing to the vast variety of secondary metabolite(s) with inherent antimicrobial/ immune

modulatory properties [10]. There is an added advantage of utilizing plant extracts as an alternative, owing to their holistic approach in countering microbial loads/infections. In addition, herbals have also exhibited synergistic action with existing antibiotics, augmenting their activity against evolving microbes [11]. Using this approach of multi herb mixtures, combinations and formulations, it is now possible to potentiate obsolete antibiotics and hinder emergence of drug resistance microbes, thereby drastically reducing the ever growing burden of development of new antibiotics in a longer run [12].

The analogous research attempts globally on both herbals and antimicrobials provides vast amount of web based data that requires to be scrutinized systematically towards a rational conclusion for further *in vitro* and *in vivo* validation. Our group has focused on utilizing 'Herbal informatics' as a novel systematic approach that allows focused herbal drug discovery with an ease at an enhanced pace [13]. It is a matrix based approach followed by molecular docking, bioactivity prediction and toxicity analysis. MDR microorganisms with a significantly higher virulence could be selected as a prime target to validate this approach. The pre-requisite need for the selection of new ligands/herbals against newly evolving pathogens relies on the development of an e-herbal archive. Presently, herbal research is facing a major challenge of batch-to-batch variation and non-reference efficacy linked data. Rapid advances in the information technology can automate the system to design and develop newer formulations exhibiting a broad spectral range against dreadful microbes, thereby offering an incredible improvement in the pace of novel drug discovery.

Our group was able to identify the main virulence factors (physiological drug targets) which could be utilized for the development of newer therapeutic alternatives as β -lactamase (Carbapenem Resistant *Escherichia coli*); Clumping factor A (Methicillin Resistant *Staphylococcus aureus*); Capsular polysaccharide (MDR *Klebsiella pneumoniae*); Efflux pump (MDR *Acinetobacter baumannii*); Biofilm formation (MDR *Pseudomonas aeruginosa*) and Hemolysin (Vancomycin Resistant *Enterococci*). Out of a database of 300 herbals, 05 herbals namely *Berberis aristata*, *Camellia sinensis*, *Cyperus rotundus*, *Holarrhena antidysenterica*, *Andrographis paniculata* exhibited highest fuzzy set scores, significant E values of docking against beta lactamase enzyme and also fulfilled the criteria of being non-toxic and non-mutagenic (as predicted by Toxicity Estimation Software Tool). Also, these herbals were found to be effective when tested at *in vitro* and *in vivo* levels. The analysis revealed that the major mechanistic aspects for providing antimicrobial efficacy and antibiotic resistance modifying abilities to these extracts were adhesion, quorum sensing and biofilm inhibition; beta-lactamase inhibition; hemolysis and hem agglutination inhibition and bacterial cell membrane disruption.

The coupling of the present model with the metabolomics approaches will unveil the hidden nodal points in the metabolic pathways controlling the overall antimicrobial efficacy of the extract in the mammalian system at different sites of action. Additionally, in comparison to lack of any specific target in re-emerging pathogens like Ebola or Zika virus, natural products can also be screened as an altogether holistic alternative using this herbal bio prospection model[14-17].

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