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Plant - Based Antibiotic Adjuvants - A Roadmap to Combat Antibiotic Resistance

Multidrug-resistant bacteria have now emerged as a global threat due to the emergence of new or re-emergence of old pathogens. This alarming situation demands either to find new/modified effective antibiotics or alternatives to reduce the overall load of infectious diseases both in the veterinary and public domain. Antibiotic adjuvants are non-antibiotic compounds that potentiate the existing antibiotic activity. The Himalayan region being a big basket and hot spot of biodiversity, inhabiting a diverse flora of medicinal plants/herbs can be evaluated for antibiotic adjuvants. These adjuvants work either by blocking the main bacterial resistance mechanisms or enhancing the antimicrobial action of the drug. The adjuvants assist in polypharmacy on bacteria by de-energizing the efflux pump channel of bacteria to escape antibiotic action and by allowing antibiotics to have greater internal access. Thus, the plant-based antibiotic adjuvants have the potency to re-empower the existing antibiotics, restoring their activities against target pathogen that too with minimal side effects/toxicity being natural in origin.

INTRODUCTION

In the global scenario, developing countries like India have been surveyed as a major consumption unit for antibiotics with the highest consumption rate of 7.5 units per person. In 2010, the total antibiotic consumption of India was highest at a rate of 12.9 x 109 units followed by China (10.0 x109 units) and the US (6.8 x109 units) [Laxminarayan and Chaudhury, 2016]. It has been further reported that BRICS countries (Brazil, Russia, India, China, and South Africa) are the main consumers of antibiotics and have contributed almost 76% to an

overall increase in consumption during the last decade out of which India shares 23% (Van Boeckel et al., 2014). Further, as per reports of Washington-based Center of Disease Dynamics, Economics and Policy (CDEEP), the percentage change in total use of antibiotics has been about 47.40% between 2010 and 2020. Due to the non-judicial use of antibiotics, antibiotic resistance has emerged as a major issue of concern. Consequently, multidrug-resistant (MDR) bacteria have now emerged as a global threat in the 21st sanctuary, as doctors are running short of potent antibiotics against them, resulting in 13 million deaths every year due to the emergence of new or re-emergence of old pathogens (Kourtesi et al., 2013). This alarming situation demands either to find new/modified effective antibiotics or the alternative one to reduce the overall load of microbes both in the veterinary and public domain.

Antibiotic adjuvants have the properties to enhance the efficacy of existing antibiotics. The concept of antibiotic adjuvant can be clearly understood with the example of clavulanic acid in combination with amoxicillin which is a widely used medicine both for humans as well as for veterinary practices. Though the clavulanic acid exhibits weak antibacterial activity, but inhibits β-lactamases and potentiates the antibacterial activities of amoxicillin. (Gibbons et al., 2003). Antibiotic adjuvants from Buxus sempervirens and *Cytisus striatus* (isoflavonoids) have been recently identified by Abreu et al. (2016; 2017) as antibiotic adjuvants against MRSA. Similarly, triterpenoids from *Taraxacum officinale* have been reported to be effective against uropathogenic bacteria (Díaz et al., 2018).

Several plant metabolites are being investigated for their antibacterial activity and their mechanism of action has been studied (Gibbons et al., 2004; Kang et al., 2011; Abreu et al., 2012). But the pharmaceutical/clinical applications of plant-derived antimicrobials are very few, despite having antibacterial efficacy due to weak or moderate activity with minimal inhibitory concentrations (MICs) typically in the range of 100–1000 μg/mL (Tegos et al., 2002). Therefore, a therapeutic contribution can be enhanced by purifying and identifying the bioactive compounds responsible for antibacterial activity to harness their probable use as antibiotic adjuvants (Abreu et al., 2017).

Since, Indian Himalayan region especially, North Western Himalayan is a big basket and hot spot of biodiversity, inhabiting a diverse flora of medicinal plants/herbs (Samant et al., 2007) is a promising source of antimicrobial bioactive compounds owing to their phenolics, flavonoids, isoflavonoids content and many more unidentified compounds (Vidyarthi et al., 2013; Sharma et al., 2014; Thakur et al., 2016). The defense system of plants can be tapped to potentiate the antibacterial effects of available antibiotics and for their possible to act as antibiotic adjuvants. WHO has published a list of bacteria for which there is an urgent need of new antibiotics among which *Escherichia coli* and *Staphylococcus aureus* are on the priority list (WHO, 2017). Nowadays, antibiotics like ciprofloxacin (fluoroquinolone), tetracycline, cefixime (3rd generation cephalosporins), ampicillin (β-lactam) have limited use, due to increased bacterial tolerance. The efficacy of such antibiotics can be enhanced in combination with antibiotic adjuvants. For example, isoflavonoids from *Cytisus striatus* with strong efflux inhibitory activity have been proven to be possible adjuvants for erythromycin against MRSA (Abreu et al., 2017). Many mechanisms like active efflux of antibiotics by bacteria mediated by efflux pumps have been suggested to be a key mechanism in bacterial resistance to many antibiotics. The identification of a probable mechanism of action against bacteria is the most important step to bring them to use in the therapeutic/pharmaceutical industry. Thus, modification of existing antibiotics by combining them with potential antibiotic adjuvants could be a possible way to tackle the resistant bacterial strains of human and animal origin.

CONCLUSION

The current scenario of emerging antibiotic resistance and re-emerging diseases has necessitated the finding of ameliorative measures to reduce the infectious load and combat antibiotic resistance. The Himalayan bioresources may be explored for antibiotic adjuvants to boost antibiotic pharmacy with minimal negative effects. Antibiotic adjuvants being potentiators may enhance the existing efficacy of the antibiotics and make them effective against resistant microbes.

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