Medicinal plants against antimicrobial resistance

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Abstract: The causes of antimicrobial resistance (AMR) are complex and may be rooted in the practices of healthcare professionals and patient's behaviour towards the use of antimicrobials as well as supply chains in the population mainly in developing countries. It is well known that any use of antimicrobials however appropriate and justified, contributes to the advancement of resistance, but widespread unnecessary and excessive use makes the situation worse. Misuse of antimicrobials is promoted in developing countries by their accessibility over the counter, without prescription and through unregulated supply chains. In developing countries, poverty is a major root factor of antimicrobial misuse, while even among the rich, some patients miss doses either by mistake or deliberate, especially in cases where signs and symptoms begin to subside after an initial favourable therapeutic response. So, this paper aims to describe for awareness of these health-seeking behaviours that lead to the threat of AMR and healthcare practices that drive the development of AMR in developing countries and discuss alternatives for disease prevention as well as other treatment options worth exploring. The chapter also highlights the use of plant-based antimicrobial as preventive agents.

Keywords: Antimicrobial, poverty, therapeutic, awareness, medicinal plants

Introduction: Antimicrobial resistance is one of the major public health problems globally, especially in developing countries (Kumar et al. 2013; Kumar and Jena 2014). Understanding the scientific basis of antimicrobial resistance is important to striving this public health threat. This should cover the resistance mechanisms, enabling novel access to diagnostics and therapeutics, through to the drivers of antimicrobial resistance in society and the environment (Figure 1; Holmes et al. 2016). The excessive utilization of antibiotics has led to the rise of antimicrobial resistance, which possess a major threat to individual health globally. At least 700,000 deaths globally a year are caused by drug-resistant

diseases and the rate of fatality has been predicted to grow to 10 million deaths per year by 2050. Antimicrobial resistance (AMR) occurs when microorganisms such as bacteria develop resistance to an antimicrobial agent. The factors causing the growth of resistance include limited knowledge and awareness of antibiotics, as well as inadequate education regarding antibiotic usage of the prescriber. Improper use, such as imperfect antibiotic treatment, reuse of leftover medicines, incorrectly taking antibiotics for the treatment of viral infections, self-medications, and skipping of doses has been reported. Indeed, many studies have implied that patients sometimes do not fully consent with the antibiotic regimen. This may result in the failure of treating the condition as well as creating resistance. Due to the emergence of resistance, the strength to treat distinct infectious diseases becomes less effective thus causing treatment failure, increasing health care cost, and even leading to death (Shapawee et al. 2020).

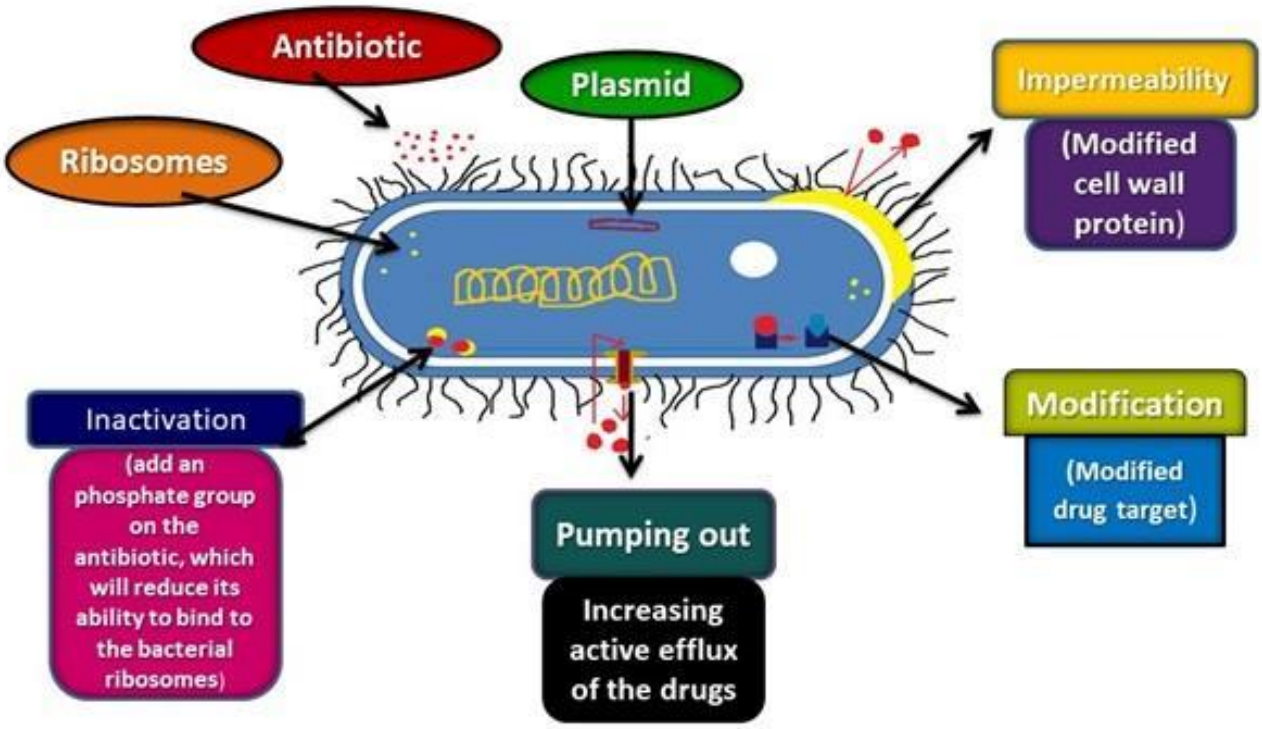

Figure 1: Mechanism of antimicrobial resistance (AMR)

As per studies, the review on antimicrobial resistance, commissioned by the UK government, argued that AMR could kill 10 million people per year by 2050. One major challenge to tackling AMR is understanding the true burden of resistance, particularly in locations where surveillance is minimum and data are sparse (Murray 2022). Numerous organizations, like the Centres for Disease Control

and Prevention and World Health Organisation (WHO) have declared antibiotic resistance to be a "Global Public Health Concern". The World Health Assembly requested WHO to propose a global action plan to fight the AMR problem. In developing countries, the causes of AMR are intricated and may depend upon the health care professionals and patient's behaviour towards the antimicrobial uses as well as supply chains of antimicrobials in the population. There is incompetent patient education, inappropriate prescription practices, limited diagnostic facilities, unauthorized sale of antimicrobials, lack of appropriate functioning drug regulatory mechanisms and nonhuman use of antimicrobials such as in animal production may include. To better accede the sources of AMR, we need to understand the various sequential steps included for a drug to get to a patient and the ultimate use, which include; prescription, distribution, production, dispensing and finally consumption of the drug by the patient or use in animal production. Accordingly, any ill-considered practice along this flow may result in the appearance of resistance (Ayukebong et al. 2017). Tackling AMR is core to the long-term economic development of countries and our well-being. To stop the global rise of drug-resistant infections, there is a supply and demand problem that needs to be fixed. The supply of new medicines is insufficient to keep up with the increase in drug resistance as older medicines are used more widely and microbes evolve to resist them. At the same time, huge quantities of antimicrobials, in particular antibiotics, are wasted globally on patients and animals who do not need them, while others who need them do not have access.

Recommended ways to tackle AMR: Some fundamental change is required in the proper way that antibiotics are prescribed and consumed, to conserve the adequacy of existing products for longer and to reduce the urgency of discovering new ones. So hereby firstly, the specific steps to reduce demand are:

1. A massive global public awareness campaign.
2. Improve hygiene and prevent the spread of infection.
3. Improve global surveillance of drug resistance and antimicrobial consumption in humans and animals.
4. Promote new, rapid diagnostics to cut unnecessary use of antibiotics.
5. Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment.
6. Use medicinal plants to prevent the infections.

Tackling antimicrobial resistance requires a wide range of approaches and developing alternatives to antibiotics. Vaccines have a vital role to play in combating drug resistance, by preventing infections in the first place. A selection of alternative products that are under development, could be used for prevention or therapy.

1. Phage therapy- Natural or engineered viruses that attack and kill bacteria.
2. Lysins- Enzymes that directly and quickly act on bacteria.
3. Antibodies – Bind to bacteria or their products, restricting their ability to cause diseases.
4. Probiotics – Prevent pathogenic bacteria from colonizing the gut.
5. Immune stimulation – Boosts the patient's natural immune system.
6. Peptides- Non-mammalian animal's natural defences against infection.

Tackling AMR in India: India has one of the highest rates of resistance to antimicrobial agents used both in humans and food animals. Specific socio-economic and cultural factors prevalent in India make the containment of resistance more challenging. Injudicious use of antimicrobials and inadequate treatment of waste waters are important drivers of AMR in India. Efforts to combat AMR have been initiated by the Indian health authorities but are still at the preliminary stages. According to the reported statement, in India, the rates of all these three sectors (human, animal and environmental parameters) have been rising disproportionately in the past decades. Another issue is the lack of sufficient research and paucity of data that not only trammel the assessment of the accurate rise and extent of AMR in India but also prevents a nationwide comparison (Taneja and Sharma 2019).

The current magnitude of the problem in India is as follows:

AMR in Man: From the 'Scoping report on antimicrobial resistance in India (2017)', under the aegis of government of India, among the Gram-negative bacteria, more than 70 % isolates of *Escherichia coli, Klebsiella pneumoniae* and *Acinetobacter baumannii* and nearly half of all *Pseudomonas aeruginosa* were resistant to fluoroquinolones and third generation cephalosporins (Gandra et al. 2017).

AMR in food & animals: As per statistics of 2015, India was the largest producer of milk and the second largest producer of fish in the world. Further, the poultry consumption in India is expected to rise by 577 % between year 2000 and 2030. With such a huge potential of food animal industry, antimicrobial agents are being used in abundance to increase the productivity. India, where a huge quantity of fish is produced in a year, is becoming an important hub of aquaculture industry. Commonly Tilapia fish found in the lakes of Maharashtra, 48 % *Enterobacteriaceae* isolated from the gut were ESBL producers. *Vibrio cholera* and *V. parahaemolyticus,* isolated from the retail markets of shrimps, shellfish and crabs in Kerala were 100 % resistant to ampicillin (Taneja and Sharma 2019).

AMR in environment: Antimicrobial-resistant bacteria and their genes have been reported from different water bag of India. The rate of isolation of *E. coli*

resistant to third generation cephalosporin was 25, 70 and 90 % when the inlet to the treatment plant was domestic water alone, domestic waste along with hospital effluent and hospital effluent alone respectively. The groundwater and surface water that are used for drinking and recreational purposes have been reported with 17 % rate of *E. coli,* resistant to third-generation cephalosporin, in central India, 7 % in North India, 50 % in East India and 100 % in South India (Purohit et al. 2017; Taneja and Sharma 2019).

Medicinal plants & AMR: About 21,000 plants listed by WHO which are extensively used for medicinal purposes throughout the world. In India, about 2500 species have been discovered, out of which about 150 are used commercially on a large scale by the biopharmaceutical companies as mainstream medicine. Therefore, India is the largest producer of medicinal plants and owns the title "*The Botanical Garden of the World* ". Plants synthesize secondary metabolites and phytochemicals and have great potential to act as therapeutics (Uttpal et al. 2019). In the last decades, research has increased to discover medicinal plants to be used synergistically with synthetic drugs, reducing side effects (e.g., *Astragalus membranaceous* on neutropenia, *Cannabis sativa* to reduce the dosage of opioids, and caffeine to reduce the dosage of nonsteroidal anti-inflammatory drugs against pain). Moreover, medicinal plants can also play an important role against the insurgence of antibiotic resistance both directly for their antimicrobial activities (e.g., antibacterial, antiviral, antifungal and antiparasitic ones) and indirectly by minimising the resistance against antibiotics (Kumar et al. 2017; Kumar and Jena 2017). The most common medicinal plants having antimicrobial potential are *Dendrophthoe falcata, Dentella repens, Dioscorea bulbifera, Gloriosa superba, Hibiscus sabdariffa, Drosera indica, Bacoppa monnieri, Andrographis paniculata, Nyctanthes arbor-tristis, Solanum virginianum* etc., (Plate 1; Plate 2). Analyses on the bioactivity of medicinal plant microbiota have documented many bioactive molecules with different functions, divulging the presence of important antibiotic compounds already characterized (Kumar et al. 2013). For instance, a *Bacillus* strain isolated from stems of the Indian traditional medicinal plant *Bacopa monnieri* showed an inhibitory effect on the growth of phytopathogenic fungi *Rhizoctonia* and *Phytophtora* species (Choudhary et al. 2022).

In the recent years, several high-quality clinical studies have assessed the ability of various infection control measures in reducing the burden of antimicrobial resistance. Addressing the problem of antimicrobial resistance requires both infection control and regulation of antibiotic use. Mounting evidence shows that control of the use of broad-spectrum antibiotics and implementation of infection control measures can result in decrease incidence of antibiotic-resistant bacteria.

Plate 1: Some common medicinal plants having antimicrobial activities. 1) *Dendrophthoe falcata;* 2) *Dentella repens;* 3) *Dioscorea bulbifera;* 4) *Gloriosa superba;* 5) *Hibiscus sabdariffa;* 6) *Drosera indica*

Plate 2: 7) *Nyctanthes arbor-tristis;* 8) *Bacoppa monnieri;* 9) *Andrographis paniculata;* 10) *Solanum virginianum*

Several reports from professional organisations and a consensus of experts have outlined strategies for the control of resistance in hospitals, with specific measures identified for antibiotic control and infection control. Various infection control strategies have been established for decades to reduce transmission of AMR and control of nosocomial infections. These measures include standard precautions, contact precautions, and isolation and decolonisation for carriers of AMRs. The objective is to review the role of infection control measures, excluding antibiotics stewardship programs, in reducing the burden of resistance (Bebell and Muiru 2014). Firstly, there should be an integrated approach between the provider and consumer sides to effectively prevent the antimicrobial resistance. From the provider side policy makers, planners, practitioners and prescribers, pharmacists and dispensers, institution managers, diagnostic and pharmaceutical industries, department of animal husbandry and from the consumer side patients and community is important in this regard. The implementation of national efforts to prevent and contain antimicrobial resistance should be through a multi-sectorial national steering committee headed by the senior -most health executive and facilitated through advisory or expert groups (Kumar et al. 2013; Ranjalkar and Chandy 2019).

Future aspects of medicinal plants in India against AMR: Indiscriminate use of antibiotics that often results in the development of side effects and drug resistance in the disease-causing factors tends the need to search for ultimate approaches for combating the infectious diseases (Pandey and Agnihotri 2015). According to studies, in the upcoming future, more people may also die from secondary bacterial infections that are resistant to antibiotics and at that time, antibiotics did not exist. In this perception, findings of new antimicrobials of plant origin, as reliable source of antibiotics, has received attention of the scientific community. So, the major ambition should be to reduce the incidence of infection, to optimize the use of antimicrobial medicines, to ensure sustainable investment in countering antimicrobial resistance. And we should give priority to the natural or herbal medicinal plants and access the therapeutic knowledge of indigenous people to act as remedial treatments that contribute to reduce AMR, as medicinal plants have been recognised as a great source of bioactive compounds and potential antimicrobials in a strategic manner with a note on prospects the focus of this chapter.

Conclusion: The chapter conclude that AMR is a serious problem throughout the world and need to address it in root level. The uses of medicinal plants and herbal products should increase to fight against AMR.

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