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Review article

Antimicrobial resistance and synergy in herbal medicine

Lorna Mundy, Barbara Pendry, Mukhlesur Rahman*

Medicines Research Group, School of Health, Sport and Bioscience, University of East London, Water Lane, Stratford, London E15 4LZ, UK

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ABSTRACT

Antimicrobial resistance (AMR) is a serious and growing threat to human health. The development of new antibiotics is limited and slow. The tradition of synergy in herbal medicine is being used as a source of research ideas. A literature review of antimicrobial research and plant synergy published in a five year period was carried out using online databases. The *in vitro* findings were that most of the research reported synergy both within plants and between plants and antibiotics. Whole plant extracts and combinations of compounds were shown to be more effective antimicrobials than isolated constituents. The discussion highlights that the *in vitro* herbal research findings are difficult to apply to practice and are not progressing to clinical trials. Collaborative, innovative, inter-disciplinary clinical research is recommended.

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1. Introduction

Health professionals, governments and international organisations are increasingly reporting the risks of antimicrobial resistance (AMR) to global health security. At a low estimate antibiotic resistance is currently causing 700,000 deaths worldwide annually, with this figure projected to reach 10 million by 2050 (O'Neil, 2014). The European Centre for Disease Prevention and Control (ECDPC) recently reported significant and increasing multiple drug resistance (MDR) in *Escherichia coli* and *Klebsiella pneumonia* in more than a third of the countries that they report on

Abbreviations: AMR, antimicrobial resistance; DOH, Department of Health; DEFRA, Department for Environment; EBM, Evidence Based Medicine; ECDC, European Centre for Disease Prevention and Control; EHTPA, European Herbal and Traditional Practitioners Association; EPI, efflux pump inhibitors; FIC, fractional inhibitory concentration; MIC, minimum inhibitory concentration; MDR, multiple drug resistance; MRSA, methicillin resistant *Staphylococcus aureus*; WHO, World Health Organisation.

* Corresponding author.
E-mail address: m.rahman@uel.ac.uk (M. Rahman).

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(ECDPC, 2015). AMR increases the duration of illness and risk of death and has been predicted to make modern medical care impossible (Davies, 2013) with surgery and chemotherapy potentially becoming high risk interventions.

The World Health Organisation (WHO) reports that there are internationally high levels of AMR in common bacteria alongside limited understanding and uncoordinated surveillance of AMR (WHO, 2014a,b). There have been just two new classes of antibiotics developed in the last 40 years. The development pipeline is slow and although two new Cephalosporin combinations are expected to be licensed in Europe soon for use in humans, AMR will also emerge for these (O'Neil, 2015). Bacterial mechanisms for resistance are innate but the high correlation between antibiotic use and AMR is clear (ECDPC, 2015). Further research, development of collaborative working, novel approaches to prevent and treat infections and the exploration of possibilities for enhancing immunity (in relation to infection by bacteria) including using prebiotics and probiotics have been recommended (DOH and DEFRA, 2013). Research and approaches for improving human immunity and resilience have been lacking (EUROCAM, 2014). WHO (2012) advises innovation and testing natural products to address AMR.

1.1. Antimicrobial resistance

Bacteria are prokaryotic micro-organisms, some of the earliest life forms, which created planetary conditions hospitable to animal life. There have been debates since the nineteenth century about whether diseases are caused by bacteria or the environment of a vulnerable, internally imbalanced body (EUROCAM, 2014). The dominant narrative of human relationship with bacteria has been the germ theory of disease which posited bacteria as enemies and motivated a war on them (Amyes, 2001). Kourtesi et al. (2013) wrote of a subsequent mind-set that this war had later been won with the discovery of antibiotics. Antimicrobial refers to a substance with inhibitory action on either the growth or survival of micro-organisms (Davies, 2013). More specifically, antibiotics are naturally derived, largely antibacterial agents (Markovitch, 2010). A bacterium has intrinsic mechanisms for protection. The thick hydrophobic outer membrane of Gram negative bacteria and mycobacteria contributes to a greater resistance than Gram positive bacteria (Stavri et al., 2007). Efflux pumps remove toxins including clinical antibiotics out of the bacterium's cells. Increased production of efflux pumps is considered a main mechanism of bacterial resistance (Junio et al., 2011) particularly for multi-resistant Gram negative bacteria (Levy, 2002; Garvey et al., 2011; Betts et al., 2012) Efflux pump inhibitors (EPI) are being researched to enable future efficacy of antibiotics but Buhner (2002) and Levy (2002) caution of the danger of this approach due to the ability of bacteria to quickly evolve into more harmful forms.

A variety of factors, including over reliance on antibiotics in healthcare and farming have caused bacteria to evolve and develop additional mechanisms of bacterial resistance in order to survive (Levy, 2002). It is well recorded but not fully understood how multiple drug resistance (MDR) can be developed in bacteria in a human or animal body through two weeks use of just a single antibiotic. 'It is almost as if bacteria strategically anticipate the confrontation of other drugs when they resist one' (Levy, 2002). The surprising extent of transferable drug resistance between different species of bacteria is understood to occur through horizontal genetic transfer of mobile traits (Smillie et al., 2011).

Blaser (2014), director of the Human Microbiome Project at New York University, describes how the trillions of microbes which have co-evolved to live with a species make up its microbiome. Blaser (2014) reports that 70–90% of cells in a human body are microbial symbionts, carrying out a range of important metabolic and protective functions. Gilbert et al. (2012) reported that in contemporary biology symbiosis is a core principle. They state that the old views of the immune system as 'defence,' 'weaponry' and 'self/non-self discrimination' are being inverted as it is increasingly understood that the microbiome co-creates the immune system (Gilbert et al., 2012). In symbiotic biology, dynamic co-evolution with microbial symbionts is important to all mammals and research is finding ever greater microbial diversity and increasingly complex interrelating (Gilbert et al., 2012). In all ecosystems diversity is crucial. After 30 years researching bacteria and human disease, Blaser (2014) argues that overused medical interventions (particularly antibiotics) have reduced the diversity of the human microbiome with damaging consequences to human health. In contrast to the understandings which led to the so called war on bacteria, contemporary research appears to be in the early stages of facilitating a paradigm shift in understandings of the human microbiome.

1.2. Plants and bacteria

Plants can be described as complex, adaptive, synergistic systems (Niemeyer et al., 2013). The low levels of infectious diseases found in wild plants, in contrast to crop plants (Hemaiswarya et al., 2008) have been attributed in part to synergistic effects of multiple mildly antibacterial constituents and other hypothesised actions such as EPI (Buhner, 2012; Brown, 2015). Plants are understood to have co-evolved with pathogens and therefore developed effective chemical responses (Datta et al., 2011). Plants in the wild are found to exhibit moderate antibacterial activity rather than entirely destroy the infectious species (Buhner, 2002). Plants and bacteria share a 'genetic fluidity' whereby they can respond to environmental stressors by rearranging their genotype (Buhner, 2002). Kourtesi et al. (2013) state that plants respond to microbial threat significantly differently to the microbes which produce antibiotics, with plants instead evolving a complexity of synergists and toxins. Buhner (2012) observes the developing resistance of malaria parasites to artemisinin, a constituent of *Artemisia* spp. and argues that this will always happen with single constituent drugs whatever their origin.

1.3. Synergy

From a scientific perspective the challenge of synergy is that the concept, by its definition, lies outside the current belief that wholes, in this context a whole plant extract, can be understood by the isolation and analysis of its parts. Plant synergy is not considered a rational approach to the combination of molecules. Numerous mathematical models have been proposed in the quest for a quantitative measurement of synergy, the definition of which tends to be defined by the precise mathematical method used to demonstrate it. Berenbaum (1989) and Greco et al. (1995) review these methods which, because they were mainly designed to assess the interaction of pharmaceutical drug combinations, do not take into account the multiple compounds, actions, interactions and effects of whole herb preparations and formulae. Williamson (2001) in a review on plant synergy cited the isobole method as proposed by Berenbaum (1989) as the current method of choice.

Combination antimicrobial therapy, with some synergistic effects, is used successfully in chemotherapy, malaria and TB treatment and other specific scenarios but is not supported by the evidence for Gram negative bacterial infections (Tamma et al., 2012). It is recommended for Gram negative bacterial infections that the bacteria are rapidly identified and targeted in order to save future use of antibiotics (Tamma et al., 2012).