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Herbal solutions to Antimicrobial Resistance

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Introduction

Antimicrobial resistance (AMR), or drug resistance, develops when microbes, including bacteria, fungi, parasites, and viruses, no longer respond to a drug that previously treated them effectively.Andrew Duong (2015) based on the antibiotic resistance report by WHO (2015) suggested 6 main causes of antibiotic resistance that have been linked to over-prescription of antibiotics, patients not finishing the entire antibiotic course, overuse of antibiotics in livestock and fish farming, poor infection control in health care settings, poor hygiene and sanitation and absence of new antibiotics being discovered (Llorand Bjerrum, 2014). The next pandemic will not be of some specific disease but due to ineffectiveness of available drugs to cure even small cuts and wounds because the parents' generation will have squandered drug effectiveness through reckless handling of antimicrobials.

Causes of antimicrobial resistance

As soon as scientists introduce a new antimicrobial drug, there is a good chance that it will become ineffective at some point in time.Microbes can change some of their characteristics to become resistant to common antimicrobial agents. This is due primarily to changes occurring within the microbes.These changes can come about in different ways:

Mutation: When microbes reproduce, genetic mutations can occur. Sometimes, this will create a microbe with genes that help it survive in the face of antimicrobial agents.

Selective pressure: Microbes that carry these resistance genes survive and replicate. The newly generated resistant microbes eventually become the dominant type.

Gene transfer: Microbes can pick up genes from other microbes. Genes conferring drug resistance can easily transfer between microbes.

The sessile formsincrease the resistance of the pathogenic bacteria to not only the host immune system but also to external agents, such as antibiotics up to 1000 times(Bassegoda, et al, 2018). Microbes adapt themselves to resist multiple antimicrobials including the 'last-line' drugs are often called "superbugs". Some of them are Multi resistant *Staphylococcus aureus* (MRSA), Vancomycin Resistant *Enterococci* (VRE), 25 percent of *Haemophilus influenzae* resist the most commonly used antibiotic, *E-coli* resist the most commonly used cure, Amoxycillin, Multi-drug resistant TB, Acyclovir-resistant HSV and Fluconazole resistant *Candida.*

Overcoming Antibiotic Resistance

- Complete and correct use of antibiotics as prescribed.
- Administration of antibiotic treatment to animals strictly by a veterinarian
- Appropriate use of vaccines on an individual or group basis for prevention of disease
- Recommended Homeopathic, herbal or other non-antibiotic alternative treatments
- Animals treated with an antibiotic must not be slaughtered or used to produce milk before withdrawal period of the antibiotic used.

Why herbal solution to AMR??

Ancient medical texts from different cultures point to herbal solutions for treatment of various diseases and disorders such as *Eber's Papyrus*, an ancient Egyptian scroll that dates back to 1500 BC; Atharva Veda consisting of Ayurveda scriptures of Hinduism 1200 BC - 1000 BC; Shen Nong Ben Cao, a Chinese medical text from 200 BCE; Dioscorides' *De Materia Medica*, which documents the Mediterranean pharmacopoeia from 50–70 CE; Bilad el-Sham herbal medicine of the Middle Eastern region between the 14th and early 20th centuries; Myrrh and frankincense mention in the Bible.

Herbal medicines have been used as antimicrobials for thousands of years, yet remain effective.Suggests that bacteria, fungi and viruses have a reduced ability to adapt to a plant derived antimicrobial regime.

Herbal solution

Plants produce complex suites of compounds known as secondary metabolites, which are not necessary for their primary growth and function, but rather serve another role of enhancing likelihood of survival. Plants are sessile and thus highly dependent on the ability to produce and release these chemical signals into their environment for the purposes of communication and defence. These substances serve as plant defence mechanisms against predation by microrganism, insects and herbivores.Plant derived antimicrobial PDA_m substances are plant-originated secondary metabolites and have great concern because of their antibiotic activity without conferring resistance (Srivastava*et al,*2014). Plants make up only a tiny percentage of the current repertoire of FDA-approved antibacterial drugs (Patridge *et al,* 2016). Before the golden era of antibiotics (1950), plant natural products represented more than one-fifth (22%) of all new molecular entities used in medicine. However, since then, there has been a decline in botanical compounds used in Western medicine (8.7%). Specific to antibacterial agents, natural products and their derivatives make up 69% of all FDA-approved drugs. The majority of these come from microbes (97%), with plant products contributing just 3% to this group (Quave, 2016).

Plants have unlimited ability to produce wide variety of secondary metabolites most of which are aromatic compounds including alkaloids, glycosides, terpenoids, saponins, steroids, flavonoids, tannins, quinones and coumarins.Alternatives to synthetic drugs that cause side effects to biological system and environment (Yeabyo*et al*, 2018). In the western world, as the people are becoming aware of the potency and side effect of synthetic drugs, there is an increasing interest in the natural product remedies with a basic approach towards the nature (Verma and Singh, 2008)

Natural antimicrobials were able to substantially decrease the MIC of antibiotics in a diverse group of bacteria containing genetic elements responsible for drug resistance. (Palaniappan and Holley, 2010). These authors studied individual activity of natural antimicrobials (eugenol, thymol, carvacrol, cinnamaldehyde, allyl isothiocyanate) and activity when paired with an antibiotic using broth microdilution and checkerboard methods. The natural antimicrobials tested were either synergistic or showed no interaction with antibiotic activity. Gram positive bacteria were more sensitive to the natural antimicrobials than the Gram-negative organisms when tested individually and in paired combination with antibiotics. *S. pyogenes* was highly resistant to erythromycin but was found to be more sensitive to the natural antimicrobials than the other microbes tested. Thus, their results showed that natural antimicrobials were able to substantially decrease the MIC of antibiotics in a diverse group of bacteria containing genetic elements responsible for drug resistance.

Nature's Pharmacopoeia

Quave (2016) classified antimicrobial compounds made by plants into 4 major groups phenolics and polyphenols; terpenoids and essential oils; lectins and polypeptides and alkaloids. Ionela and Ion, 2007 has described phenolics and polyphenol, quinones, flavones, flavonoids, flavonols, tannins, coumarins, terpenes, essential oils, lectins, polyphenols, alkaloids, monosaccharide fructose, polyacetylenes, polyamines, isothiocyanates, thiosulfinates, glucosinates having antimicrobial properties in various plants. All of the identified components from plants active against microorganisms are aromatic or saturated organic compounds. (Cowan 1999)In general, plant derived antimicrobials (mostly secondary metabolites) are phenol derivative, sufficiently able to control the microbes by reducing the pH, increasing membrane permeability and altering efflux pumping (Yeabyo*et al*,2018).

The efficiency of herbal medicines is attributed to the synergistic action of a wide variety of chemically and physiologically active components rather than a single component (Daniel *et al*,2007). For instance, thetraditional Chinese medicinal plant Qinghao is the source of antimalarial compound artemisinin, the discovery of which recently resulted in the 2015 Nobel Prize in Physiology or medicine to Chinese scientist Youyou Tu. Unfortunately, the widespread emergence of resistance to artemisinin monotherapy has become increasingly problematic. Qinghao is a therapy known to have been in use for millennia, as evidenced by specific recommendations found concerning its preparation and use in ancient text from the Jin dynasty. This begs the question: how is it that a traditional preparation in use for millennia did not yield resistance, yet isolation of a single compound for monotherapy resulted in widespread resistance in a short period of time. Interestingly, a few recent studies have demonstrated that not only do chemically complex extracts of Qinghao exhibit antiplasmodial activity that is 6-18 folds greater than what was expected based on artemisinin content alone, but whole plant therapy was effective at overcoming artemisinin resistance in animal model.(Rasoanaivo P, *et al*. 2011)

Table: Some plants containing antimicrobial activity (Cowan 1999)

COMMON NAME	SCIENTIFIC NAME	COMPOUND	CLASS	ACTIVITY
Aloe	*Aloe barbadensis, Aloe vera*	Latex	Complex mixture	*Corynebacterium, Salmonella, Streptococcus, S. aureus*

Ashwagandha	*Withaniasomniferum*	Withafarin A	Lactone	Bacteria, fungi
Bael tree	*Aegle marmelos*	Essential oil	Terpenoid	Fungi
Black pepper	*Piper nigrum*	Piperine	Alkaloid	Fungi, *Lactobacillus, micrococcus, E.coli, E. faecalis*
Blueberry	*Vaccinium* spp	Fructose	Monosaccharide	*E. coli*
Caraway	*Carum carvi*	--	Coumarins	Bacteria, fungi, viruses
Cashew	*Anacardium pulsatilla*	Salicylic acids	Polyphenols	*P.acnes*, Bacteria, fungi
Ceylon Cinnamon	*Cinnamomum verum*	Essential oils, others	Terpenoids, tannins	General
Chamomile	*Marticaria chamomilla*	Anthemic acid	Phenolic acid	*M.tuberculosis, S. typhinmurium, S. aureus, helminths*
Clove	*Syzygiumaromaticum*	Eugenol	Terpenoid	Bacteria, fungi
Eucalyptus	*Eucalyptus globulus*	Tannin	Polyphenol, terpenoid	Bacteria, viruses
Ginseng	*Panax notoginseng*		Saponins	*E. coli, Sporothrix, Staphylococcus, Trichophyton*
Grapefruit peel	*Citrus paradisa*		Terpenoid	Fungi
Green tea	*Camellia sinensis*	Catechin	Flavanoid	General, *Shigella, Vibrio, S. mutans,* Viruses
Henna	*Lawsoniainermis*	Gallic acid	Phenolic	*S. aureus*
Lemon balm	*Melissa officinalis*	Tannins	Polyphenols	Viruses
Lemon verbana	*Aloysia triphylla*	Essential oil	Terpenoid	*Ascaris, E.coli, M.tuberculosis, S. aureus*
Onion	*Allium cepa*	Allicin	Sulfoxide	Bacteria, candida
Orange peel	*Citrus sinensis*		Terpenoid	Fungi
Papaya	*Carica papaya*	Latex	Mix of terpenoids, organic acids, alkaloids	General

Quinine	*Cinchona* spp.	Quinine	Alkaloid	*Plasmodium* spp.
Tansy	*Tanacetum vulgare*	Essential oils	Terpenoid	Helminths, bacteria
Tarragon	*Artemisia dracunculus*	Caffeic acids	Terpenoids	Viruses, helminths
Thyme	*Thymus vulgaris*	Caffeic acid	Terpenoid	Viruses, bacteria, fungi
Turmeric	*Curcuma longa*	Curcumin	Terpenoids	Bacteria, protozoa

Table shows plants effective against resistant organisms(Srivastava *et al*, 2014)

PLANTS	**PLANT DERIVATIVES**	**EFFECTIVE AGAINST**
Anthrocephalouscadamba& *Pterocarpus santalinus*	Ethanolic extract	$MDRs^{M}$
Lantana camara	Leaf extract in dichloromethane & methanol	MDRs G+ve and MDRs G-ve
Butea monosperma	Ethanolic & hot water extract	$MDRs^{M}$
Jatropha curcas	Ethanolic & methanolic extract	MDRsG + ve + Micrococcusspp. &MDRsG−ve + Shigellaspp.+ Bacillus spp.
Rhus coriaria	Ethanolic extract	MDR P. aeruginosa

- $MDRs^{M}$ = *Staphylococcus aureus* + *Acinetobacter* sp. + *Citrobacter freundii* + *Chromobacteriumviolaceum* + *Escherichia coli* + *Klebsiella* sp. + *Proteus* sp. + *Pseudomonas aeruginosa* + *Salmonella typhi* + *Vibrio cholera*;
- MDRsG + ve=*S. aureus* (MRSA) + *Streptococcus pyogenes* + *Enterococcus faecalis* (VRE);
- MDRsG−ve = *Acinetobacter baumannii* + *Citrobacter freundii* + *Proteus mirabilis* + *Proteus vulgaris* + *Pseudomonas aeruginosa*

Challenges of Plants as a Source of Antimicrobials

- Tribal healers keep no records and the information is mainly passed on verbally from generation to generation (Verma and Singh, 2008).
- Plant extracts are incredibly chemically complex – much more so than fungi, for example, as a single extract preparation may contain hundreds of different chemical entities. The isolation of single compounds with the desired antimicrobial bioactivity can be time consuming and requires a large amount of bulk plant material.
- Rediscovery of the same compounds from different sources presents problems, and much attention must be paid to careful dereplication early in the discovery process in order to avoid time and effort spent chasing known molecular entities.
- Making arrangements for access to plant specimens can sometimes be difficult, especially in an international setting. Regulations concerning plant collection permits and export/import permits differ depending on where the research is being conducted. Furthermore, as per the regulations and guidance set forth by the United Nations Convention on Biological Diversity and the Nagoya Protocol, negotiation of equitable access and benefit sharing agreements is required for such research.
- Scientists from divergent fields are investigating plants anew with an eye to their antimicrobial usefulness. A sense of urgency accompanies the search as the pace of species extinction continues (Cowan, 1999).

Conclusion

While herbal solutions present a promising avenue in the fight against AMR, there are challenges to be addressed, such as the standardization of dosages, clinical validation, and ensuring safety in large-scale applications. Further research and rigorous clinical trials are necessary to fully integrate herbal remedies into mainstream healthcare as complementary or alternative treatments for antibiotic-resistant infections.

In conclusion, herbal medicine offers a natural and sustainable approach to combating antimicrobial resistance. With continued research, these remedies could become key components in a multi-faceted strategy to address the growing global health threat posed by AMR.

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