Registered office 25 Lincoln Close, Tewkesbury, GL20 5TY - Tel: 01684291605
1 November 2013

A paper from the European Herbal and Traditional Medicine Practitioners Association (EHTPA) for the House of Commons Select Committee on Science and Technology's antimicrobial resistance (AMR) inquiry.

The EHTPA is an umbrella body which represents professional associations of herbal/traditional medicine practitioners offering variously western herbal medicine, Chinese herbal medicine, Ayurveda and traditional Tibetan medicine. The EHTPA is dedicated to the development of herbal/traditional medicine, preserving and enhancing the legal basis of practice across EU Members States and promoting best practice throughout the traditions. Contact via the Chair, Michael McIntyre, ***ehpa@globalnet.co.uk*****.**

Declaration of interests; The EHTPA is dedicated to the appropriate use of herbal medicine, the development of herbal/traditional medicine, promoting best practice across the various herbal traditions. The EHTPA is a not-for-profit association.

Herbs to combat the threat of microbial resistance to antibiotics

Executive Summary

In light of growing concerns relating to microbial resistance to antibiotics increasing attention is being given to the role that herbal medicines may play as autonomous anti-bacterial agents or as adjuvant treatments used to potentiate conventional drugs. This paper selectively reviews the evidence for herbal medicine as a valuable resource to combat bacterial resistance to antibiotics and suggests that further research is warranted.

1. Synergy is an important characteristic determining the medicinal action of many herbal medicines occurring at pharmacodynamic and pharmacokinetic level [1] [2] and a number of papers have been published investigating potential benefits conferred by the synergism of phytoconstituents.[3] [4] [5] [6] In particular, researchers have demonstrated that combining antibiotics with plant medicines can enhance the action of antibiotics thereby overcoming antibiotic resistance.[7]

2. This is achieved in three main ways: firstly by means of a combined phytochemical and antibiotic attack on the bacterial cell wall - epigallocatechin gallate (EGCG) as

found in green tea and carob powder is effective in this regard. Secondly, antibiotic resistance can be overcome by inhibition of enzymes that are generated by bacteria for the deactivation of antibiotics (again EGCG is active here) or by thirdly by disabling an efflux pumping system developed by several bacteria in order to prevent potentially destructive compounds such as antibiotics from penetrating into the bacteria, or to expel the antibiotics out of the bacteria cell once they have invaded it.[8]

3. Thymol and carvacrol, two compounds in the essential oil of thyme (*Thymus vulgaris*) act as so-called 'membrane permeabilizers' enabling antibiotics to penetrate into Gram-negative bacteria.[9] Thyme also contains baicalein also present in the Scutellaria species (Lamiaceae family) and baicalein has shown significant ability to reverse MRSA resistance to the antibiotic ciprofloxacin by inhibiting the bacteria's defensive efflux pump.[10]

4. Most research to find agents to support antibiotics becoming ineffective against common bacteria has been lab-based rather than on human populations. A recent review provided evidence of 34 different herbs containing constituents known to inhibit the bacterial efflux pumps.[11] For example, *E. coli* is currently demonstrating resistance to several antibiotics but, combined with extracts of *Sophora alopecuroides,* isolates of the bacteria were found susceptible to ciprofloxacin.[12] Similarly, Klančnik et al. (2013) found that extracts of *Rosmarinus officinalis* inhibited drug resistant strains of *Campylobacter*.[13] Extracts from several other plants in this study, have shown similar inhibitory effects on *Campylobacter* as have extracts of green tea.[14]

5. Another major concern is the drug resistant bacterium, Methicillin-resistant *Staphylococcus aureus* (MRSA). Exposure to berberine, a compound found in many medicinal plants (e.g. *Coptis chinensis* and *Phellodendron amurens)* together with antibiotics such as levofloxacin and azithromycin [15] (which had recently proved ineffective against MRSA), resulted in the reactivation of the efficacy of the antibiotic drugs. Similar results were found employing *Scutellaria baicalensis* against *Staphylococcus aureus* to restore the antibacterial actions of ciprofloxacin via similar mechanisms of efflux pump inhibition.[16] Indirubin, extracted from the leaves of *Wrightia tinctoria,* used in Ayurvedic medicine, has also been found to have an inhibitory effect on *Staphylococcus aureus*.[17] Nineteen herbs commonly used in Chinese medicine have inhibitory effects of which *Dendrobenthamia capitata*, *Elsholtzia rugulosa, Elsholtzia blanda, Geranium strictipes, Polygonum multiflorum* offer promising anti-MRSA possibilities.[18] Zuo et al. investigated the antimicrobial effects of 30 plants traditionally used to treat skin infection focusing on their potential to inhibit *Staphylococcus aureus.* Of these, 21 extracts were found to have anti-MRSA effects with *M. yunnanensis* and *S. arborescens* being the most active. [19]

6. Below we provide a table reviewing some promising evidenced-based research on herbal medicines to help combat the growing threat of antibiotic resistance. This presentation is a selective review illustrating the way in which herbal medicines might make a useful contribution; it is not a comprehensive and systematic evaluation of the evidence. To produce this review searches were performed in October 2013 in AltHealthWatch, AMED, Embase, Estar, Cinahl, the Cochrane Library and PubMed.

7. To provide a practical evaluation of the evidence presented in this review we have adapted a version of the widely used GRADE approach (Grades of Recommendation, Assessment, Development and Evaluation).[20] This allows for 4 levels of rating of the research evidence - High, Moderate, Low and Very Low. For simplicity, we have amalgamated Low and Very Low grades into a single category of Preliminary evidence. This selective review highlights potentially fruitful areas for future research.

8. Herbal medicines may help to resolve the problem of antibiotic resistance more directly. Doctors faced with relatively minor, often self limiting, but common infections eg pharyngitis, laryngitis and tonsillitis or mild urinary tract infections (UTIs) have little to offer except advice on how to manage the condition or otherwise prescribe an antibiotic which may not be appropriate.

9. Herbal medicines may fill this therapeutic gap, providing effective treatment that reduces antibiotic prescribing and does not contribute to microbial resistance. For example, a number of herbal medicines are traditionally used to treat sore throat such as sage *(Salvia officinalis)*[21 22] , dyers woad *(Isatis tinctoria*)[23], echinacea (*Echinacea purpurea* or *angustifolia*) [24 25] and burdock (*Arctium lappa).*[26 27] Herbal medicine can also help to ease UTIs employing remedies such as *Arctostaphylos uva ursi* [28], [29], [30], [31]and *Zea mays.*[32] *Nigella sativa* shows promise in treating drug resistant H-pylori (see Table 1 below).

10. Other common minor infections may also be successfully treated with herbal medicines sparing use of more potent antibiotics. **This is a potentially rich territory worth exploring as a practical way of combating microbial resistance to conventional antibiotics.** Herbal medicines have been used as antibiotics for thousands of years, yet remain effective, suggesting that bacteria have a reduced ability to adapt to a plant derived antibacterial regimen.

Table 1: Herbs to help combat growing antibiotic resistance

Study Design	Publication Details	Main Findings	Possible Mechanisms	Strength of Evidence
An evidence-based systematic review of umckaloabo (*Pelargonium sidoides*) by the US Natural Standard Research Collaboration.	Ulbricht C et al. (2010) *Journal of Dietary Supplements* ;7(3):283-302.[33]	This comprehensive systematic review concluded that there was strong scientific evidence (Grade A) - including 4 good quality RCTs involving 933 participants - to support the use of pelargonium for acute bronchitis and good scientific evidence (Grade B) for the its use in acute pharyngitis and the common cold. No serious toxic effects have been observed in any trial relating to pelargonium.	Pelargonium has exhibited a marked antibacterial action against a wide range of pathogenic bacteria.	**High**
Efficacy and safety of a combination herbal medicinal product containing nasturtium (*Tropaeoli majoris herba*) and Horseradish (*Armoracia rusticana)*for the prophylactic treatment of patients with respiratory tract diseases: a randomised, prospective, double-blind, placebo-controlled phase III trial.	Fintelmann V et al. (2012). *Current Medical Research Opinion*; 28(11):1799-807.[34]	351 participants were randomly allocated to either active treatment (Group 1), a lower dose of active herbs + placebo (Group 2), or just placebo (Group 3). The maximum duration of treatment was 84 days. In the intention to treat (ITT) population excluding early infections (n = 344) the infection rates were 13.3% for Group 1, 18.4% for Group 2 and 25.6% for placebo Group 3. The statistical trend test showed significant results (p = 0.0171). The herbal combination appears to offer a prophylactic advantage which could help reduce antibiotic prescription.	These herbs contain several isothiocyanates which have a marked in vitro broad spectrum anti-bacterial action.[35]	**Moderate**

A double blind randomised control trial where 107 participants were randomised to receive either licorice root (*Glycyrrhiza glabra*) - trade name *gutgard* - or placebo for 60 days	Puram et al. (2013) *Evidence-Based Complementary and Alternative Medicine*; Article ID 263805.[36]	The results showed that 56% (n=28) were *H.pylori* negative compared to 4% (n=2) in the placebo group. In other work by the same team, the herb extract reduced symptoms of dyspepsia and there were no adverse events reported.	*Glycyrrhiza glabra* showed antimicrobial activity in vitro and anti-adhesive properties against H-pylori.[37]	**Moderate**
A randomised, double-blind, placebo-controlled trial of a herbal medicinal product Angocin Anti-Infekt N containing nasturtium (*Tropaeoli majoris herba*) and horseradish *(Armoraciae rusticana)* for the prophylactic treatment of patients with chronically recurrent lower urinary tract infections (RUTIs).	Albrecht U et al. (2007). *Current Medical Research Opinion*;23(10):2415-22.[38]	129 patients with RUTIs were randomised to active herbal or placebo treatment for 90 days. The primary outcome was the number of laboratory confirmed urinary tract infections. The per protocol mean number of recurrent UTIs in the study period was 0.43 versus 0.77 for the placebo group. This result is statistically significant (p = 0.035). A total of 36 patients in the test group and 37 patients in the placebo group reported adverse events. Two serious adverse events were reported in the placebo group and one serious adverse event in the treatment group (not associated with the study medication). This herbal product appears to be effective and safe as a prophylaxis for RUTIs.	Mustard oils (including isothiocyanates) found in these two herbs have been shown to have a broad spectrum antibacterial action.[39]	**Preliminary** (This trial needs to be repeated by independent researchers using an intention to treat analysis.)
A randomised control trial of a complex Chinese herbal medicine (San Ling Jie Du Tang) in the treatment of women with recurrent lower urinary tract infections (RUTIs)	Huang MJ. (2007). *Hubei J. of Traditional Chinese Medicine*;29:38-9.[40]	300 women were randomised in a 2:1 ratio to the Chinese herbal remedy or an antibiotic. Treatment was administered for 7 days with a 6 month follow up. 79.5% of the herbal group reported no infection in the follow up period compared	Several of the included herbs, such as tree peony bark (*Paeonia suffroticosa),* have been shown to have a broad spectrum antibacterial	**Preliminary** (Due to a lack of detail relating to the trial methodology.)

		with 49% in the antibiotic group. This was statistically significant ($p<0.05$).	action.[41]	
A Cochrane systematic review of Chinese herbs for sore throat.	Huang Y et al. (2012). *Cochrane Database Systematic Review*. 14;3:CD004877.[42]	12 studies involving 1954 participants were included in this systematic review. 6/12 studies were shown to be more effective than the control with 3 herbal remedies appearing more effective than antibiotics. The remaining 6 studies showed equivalent effectiveness to the controls.	Several of the included herbs such as Japanese Honeysuckle (*Lonicera japonica)*, have been shown to have a broad spectrum anti-bacterial action.[43]	**Preliminary** (Due to the poor methodological quality of the included trials.)
Comparative study *of Nigella sativa* and triple therapy in eradication of *Helicobacter pylori* in patients with non-ulcer dyspepsia. 88 adults with dyspeptic symptoms and positive *H.pylori* test were randomised to four groups: receiving i) triple therapy (TT) comprising of clarithromycin, amoxicillin, omeprazole [n= 23], ii) 1 g *Nigella sativa* + 40 mg omeprazole (OM) [n= 21], iii) 2 g NS + OM [n= 21] or iv) 3 g NS + OM [n= 23]. Main outcome was eradication of *H.pylori.*	Salem et al. (2010). *Saudi Journal of Gastroenterology*. 16(3):207-14.[44]	*H.pylori* eradication was 82.6% in the antibiotic triple therapy group, 47.6 with 1g of *Nigella sativa,* 66.7% with 2g and 47.8% with 3g *Nigella sativa.* Eradication rates with 2 g *Nigell sativa* and antibiotics were statistically similar. *Nigella sativa* seeds possess clinically useful anti-*H.pylori* activity, comparable to antibiotic triple therapy. Further clinical studies combining *Nigella sativa* with antibiotics are suggested by the authors.	In vitro study showed that *Nigella sativa* inhibited growth in all strains of *H.pylori* within 60 minutes of exposure.[45]	**Preliminary**

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