

The role of phytotherapy (herbal medicine) in sidestepping antimicrobial Resistance – a contribution from EUROCAM

SIDESTEPPING ANTIMICROBIAL RESISTANCE

The Role of Existing and New Antibiotics

Conference at the European Parliament hosted by MEPs Nicola Caputo and José Inácio Faria, moderated by Peter O'Donnell, 27 June 2017

Herbal medicines have been used as antimicrobials for thousands of years, yet they remain effective and this suggests that bacteria, fungi and viruses have a significantly reduced ability to adapt to a plant-derived antimicrobial regime. This is likely to be due to the synergistic effect of the orchestra of chemicals contained by medicinal plants that prevents bacteria, fungi and viruses from developing immunity to their constituents as multi-targeting by the chemical combinations increases efficacy and reduces resistance.

The antimicrobial action of each individual herbal medicine is further enhanced by the use of herb combinations routinely employed in all herbal traditional medicine systems. Synergy occurs at both a pharmacodynamic (what the drug does to the body) and pharmacokinetic (what the body does to the drug) level (Gibbs 2013; Teucher et al. 2004) and a number of papers have been published investigating potential benefits conferred by the synergism of phytoconstituents (Bishayee et al. 2012; Ricciardiello et al. 2011; Fiebich et al. 2011; Gertsch 2011; Yang et al. 2014).

Synergism can be seen at work where plant medicines are combined with conventional antibiotics to combat AMR and there is a burgeoning body of literature exploring the therapeutic possibilities of this strategy. A comprehensive review provided evidence of 34 different herbs containing constituents known to inhibit the bacterial efflux pumps and thereby potentially reactivate antibiotics to which bacteria have developed immunity (Kourtesi et al. 2013). For example, *E. coli* is currently demonstrating resistance to several antibiotics but, combined with extracts of *Sophora alopecuroides*, isolates of the bacteria were found to be susceptible to ciprofloxacin (Zhou et al. 2012). Comparable results were also found employing *Scutellaria baicalensis* against *S. aureus* to restore the antibacterial actions of ciprofloxacin via similar mechanisms of efflux pump inhibition (Chan et al. 2011).

Another major concern is the drug-resistant bacterium, methicillin-resistant *S. aureus* (MRSA).

Exposure to berberine, a compound found in many medicinal plants (eg, *Berberis vulgaris*, *Coptis chinensis* and *Phellodendron amurense*) together with antibiotics such as levofloxacin and azithromycin (which had recently been proved ineffective against MRSA), resulted in the reactivation of the efficacy of the antibiotic drugs (Zuo et al. 2012). Synergistic effects between silibinin (extracted from *Silybum marianum*) and antibiotics have also shown potential to inhibit MRSA (Kang et al. 2011). Herb-drug combinations are proving effective against other drug-resistant bacteria.

Synergistic interaction between epigallocatechin gallate (EGCg) from green tea and antimycotics such as amphotericin B and fluconazole has been reported against *C. albicans* (Hemaiswarya et al. 2008), while *Nigella sativa* and omeprazole compared favourably to triple therapy in eradication of *Helicobacter pylori* in 88 patients with dyspepsia and a positive *H. pylori* test (Salem et al. 2010).

References

- Ahmad, A., Khan, A., Akhtar, F., Yousuf, S., Xess, I., Khan, L.A., Manzoor, N., 2011. Fungicidal activity of thymol and carvacrol by disrupting ergosterol biosynthesis and membrane integrity against *Candida*. *European Journal of Clinical Microbiology and Infectious Disease*. 30 (1): 41–50.
- Bishayee, A., Thoppil, R.J., Waghray, A., Kruse, J.A., Novotny, N.A., Darvesh, A.S., 2012. Dietary phytochemicals in the chemoprevention and treatment of hepatocellular carcinoma: *In vivo* evidence, molecular targets, and clinical relevance. *Current Cancer Drug Targets*. 12 (9): 1191–232.
- Chan, B.C., Ip, M., Lau, C.B., Lui, S.L., Jolivald, C., Ganem-Elbaz, C., Litaudon, M., Reiner, N.E., Gong, H., See, R.H., Fung, K.P., Leung, P.C., 2011. Synergistic effects of baicalein with ciprofloxacin against NorA over-expressed methicillin-resistant *Staphylococcus aureus* (MRSA) and inhibition of MRSA pyruvate kinase. *Journal of Ethnopharmacology*. 137 (1): 767–73.
- Fiebich, B.L., Knörle, R., Appel, K., Kammler, T., Weiss, G., 2011. Pharmacological studies in an herbal drug combination of St. John's Wort (*Hypericum perforatum*) and passion flower (*Passiflora incarnata*): *In vitro* and *in vivo* evidence of synergy between *Hypericum* and *Passiflora* in antidepressant pharmacological models. *Fitoterapia*. 82 (3): 474–80.
- Gertsch, J., 2011. Botanical drugs, synergy, and network pharmacology: Forth and back to intelligent mixtures. *Planta Medica*. 77 (11): 1086–98.
- Gibbs, R., 2013. Evaluating the biological actions of Chinese medicinal herbs. *Register of Chinese Herbal Medicine Journal*. 10: 31–38.
- Hemaiswarya, S., Kruthiventi, A.K., Doble, M., 2008. Synergism between natural products and antibiotics against infectious diseases. *Phytomedicine*. 15 (8): 639–52.
- Kang, H.K., Kim, H.Y., Cha, J.D., 2011. Synergistic effects between silibinin and antibiotics on methicillin-resistant *Staphylococcus aureus* isolated from clinical specimens. *Biotechnology Journal*. 6 (11): 1397–408.
- Kourtesi, C., Ball, A.R., Huang, Y., Jachak, S.M., Vera, D.M.A., Khondkar, P., Gibbons, S., Hamblin, M.R., Tegos, G.P., 2013. Drug discovery and the challenge of clinical implementation. *Open Microbiology Journal*. 7 (S:1M3) 34–52.
- Ricciardiello, L., Bazzoli, F., Fogliano, V., 2011. Phytochemicals and colorectal cancer prevention--myth or reality? *Nature Reviews Gastroenterology Hepatology*. 8 (10): 592–6.
- Salem, E.M., Yar, T., Bamosa, A.O., Al-Quorain, A., Yasawy, M.I., Alsulaiman, R.M., Randhawa, M.A., 2010. Comparative study of *Nigella sativa* and triple therapy in eradication of *Helicobacter pylori* in patients with non-ulcer dyspepsia. *Saudi Journal of Gastroenterology*. 16 (3): 207–14.
- Teucher, B., Olivares, M., Cori, H., 2004. Enhancers of iron absorption: Ascorbic acid and other organic acids. *International journal for vitamin and nutrition research*. 74, 403–419.
- Yang, Y., Zhang, Z., Li, S., Ye, X., Li, X., He, K., 2014. Synergy effects of herb extracts: Pharmacokinetics and pharmacodynamic basis. *Fitoterapia*. 92: 133–47.
- Zhou, X., Jia, F., Liu, X., Wang, Y., 2012. Total alkaloids of *Sophorea alopecuroides*-induced down-regulation of AcrAB-TolC efflux pump reverses susceptibility to ciprofloxacin in clinical multidrug resistant *Escherichia coli* isolates. *Phytotherapy Research*. 26 (11): 1637–43.
- Zuo, G.Y., Li, Y., Han, J., Wang, G.C., Zhang, Y.L., Bian, Z.Q., 2012. Antibacterial and synergy of berberines with antibacterial agents against clinical multi-drug resistant isolates of methicillin-resistant *Staphylococcus aureus* (MRSA). *Molecules*. 17 (9): 10322–30.