Plant polyphenolic compounds as potential antimicrobial drugs

Recently there has been much discussion about the possibility that plant-derived phytochemical compounds may have a role as potential antimicrobial substances, and there is evidence to suggest that plant polyphenols have anticarcinogenic properties (Ferrazzano *et al.*, 2009, 2011).

Phytochemicals such as flavonoids, tea catechins, resveratrol, phenolic acids and other botanical molecular byproducts, originally produced as defensive molecules in order to discourage animals from eating plants, have recently attracted much attention by researchers and clinicians worldwide, particularly because they have proved to be excellent factors for promoting human health (Kay, 2010). Some of the health benefits gained from eating fruit and vegetables and plant-derived products are believed to be due to their polyphenol content. Elucidating the mechanisms behind metabolism of polyphenols is an important step in understanding their health effects *in vivo*. Gut absorption and metabolism of these compounds depend on their relationship with intestinal microbes. As food is the main source for the intake of plant polyphenols, this has also raised a debate about the role of plant-derived phytochemicals on the gut microflora, as they may modify the gut microbial composition and/or biological activity and, moreover, may be converted by the colonic microbiota to bioactive compounds that can influence host health (Selma *et al.*, 2009; Kemperman *et al.*, 2010). This issue underlines one aspect of a wider and more complex relationship between plant products, microbes and animal species which might hamper the interpretation of these products as real antibacterial chemicals in humans. This is also the context in which the role of plant polyphenols as potential drugs against those microbial species that are important in medical microbiology has to be addressed (Chirumbolo, 2010). Hence, the *in vivo* antimicrobial action of a plant polyphenolic compound has to face this complex biological issue.

How can we use these natural compounds as antimicrobials, therefore?

Several reports show the impact of plant-derived nutrients in preventing infectious diseases and inflammatory ailments. Tea catechins, particularly epigallocatechin-3-gallate, proved effective in treating important nosocomial bacterial infections (Gordon & Wareham, 2010), flavonoids and some phenolic acids such as caffeic acid, chlorogenic acid, gallic acid and quinic acid exert a potent antimicrobial action against typical microbial strains affecting the human respiratory or urinary tract, including *Candida* species (Özçelik *et al.*, 2011), the flavonoid galangin is able to suppress *Klebsiella pneumoniae* replication by inhibiting bacterial DnaB helicase (Chen & Huang, 2011), quercetin and resveratrol have proved effective in modulating the host response to *Salmonella enterica* serovar Typhimurium infection (Paolillo *et al.*, 2011), and the use of genistein, a well-known anti-staphylococcal agent, in combination with probiotics may augment the effectiveness of antimicrobial therapies currently used in the management of infections (Hong *et al.*, 2006).

These results appear quite encouraging but, nevertheless, most of them resulted from *in vitro* research, whilst clinical outcomes following the administration of polyphenolic substances are rarely reported in the literature, due to the many problems related to cultivar variability, chemical extraction and plant polyphenol content. The main problem when using a phenolic derivative that proves to have high antimicrobial efficacy *in vitro* and/or in animal models (Kim *et al.*, 2009) concerns its metabolic route in the organism, including its interaction with the gut microflora. The main interest in research is to highlight or clarify the role of plant polyphenols as potential immunoregulatory drugs, namely that their main action lies in the role that they play in the immune system and inflammation (by affecting signalling

pathways strategic in immune and inflammatory responses), rather than them having a direct antibacterial or antimicrobial potential. For example, when an inflammatory response was induced by treating macrophages with bacterial endotoxin, end products of polyphenol degradation, such as ferulaldehyde, exerted a beneficial anti-inflammatory response by diminishing MAP kinase activation, thereby inhibiting NF- κ B activation, mitochondrial depolarization and reactive oxygen species production (Tucsek *et al.*, 2011), similarly to many purified aglycone flavonoids (Chirumbolo, 2010). It is arguable that the antimicrobial activity of polyphenols might be due principally to their well-recognized anti-inflammatory potential. Fruits and vegetables can act as a primary source of anti-inflammatory and chemopreventive substances; however, dietary vegetables and fruits may even contain industrial antimicrobial phytochemicals. Yet another critical issue is the presence of aminoglycosidic antibiotics, such as streptomycin, in fruits commonly present in the human diet and usually considered to be rich in flavonoids, such as apples (Bohm *et al.*, 2010). Daily ingestion of food rich in plant-derived polyphenols provides an excellent solution for preventing the onset of inflammatory diseases, as most of the evidence reported for these compounds deals with their efficacy as anti-inflammatory substances; nevertheless, the efficacy of these compounds as raw components of food is far from being assessed, due to the many issues related to active molecule concentration, chemical composition, gut absorption and metabolism, and phytochemicals as contaminants. Research on the role of flavonoids as well as other polyphenols in inflammation in humans is increasing and encouraging new results have been achieved but there is still insufficient evidence for planning future clinical pharmacology trials, as *in vivo* investigation has been mainly focused on flavonoid-rich foods and not on purified

molecules. Most of the analysis lacks assessment of the phenolics content of food and beverages, as well as their absorption and bio-availability, so showing a failure to associate an antimicrobial effect with a change in plasma circulating levels of these compounds. What is the way ahead? Currently there is a lot of interest in natural herbal remedies, with mankind being encouraged to return to his ancestral relationship with the natural environment, and certainly most people are inclined to agree with taking natural products rather than drugs. Many further human trials are needed in order to clarify whether phytochemicals really represent key molecules involved in the antimicrobial potential of plant-derived foods. Further molecular and pharmacological investigation may, in the near future, reveal that they deserve a place among other well-known antibacterial and/or antiviral chemicals.

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Bohm, D. A., Stachel, C. S. & Gowik, P. (2010). Confirmatory method for the determination of streptomycin in apples by LC-MS/MS. *Anal Chim Acta* **672**, 103–106.

Chen, C. C. & Huang, C. Y. (2011). Inhibition of *Klebsiella pneumoniae* DnaB helicase by the flavonol galangin. *Protein J* **30**, 59–65.

Chirumbolo, S. (2010). The role of quercetin, flavonols and flavones in modulating inflammatory cell function. *Inflamm Allergy Drug Targets* **9**, 263–285.

Ferrazzano, G. F., Amato, I., Ingenito, A., De Natale, A. & Pollio, A. (2009). Anti-carcinogenic effects of polyphenols from plant stimulant beverages (cocoa, coffee, tea). *Fitoterapia* **80**, 255–262.

Ferrazzano, G. F., Amato, I., Ingenito, A., Zarrelli, A., Pinto, G. & Pollio, A. (2011). Plant polyphenols and their anti-carcinogenic properties: a review. *Molecules* **16**, 1486–1507.

Gordon, N. C. & Wareham, D. W. (2010). Antimicrobial activity of the green tea polyphenol (–)-epigallocatechin-3-gallate (EGCG) against clinical isolates of *Stenotrophomonas maltophilia*. *Int J Antimicrob Agents* **36**, 129–131.

Hong, H., Landauer, M. R., Foriska, M. A. & Ledney, G. D. (2006). Antibacterial activity of

the soy isoflavone genistein. *J Basic Microbiol* **46**, 329–335.

Kay, C. D. (2010). The future of flavonoid research. *Br J Nutr* **104** (Suppl. 3), S91–S95.

Kemperman, R. A., Bolca, S., Roger, L. C. & Vaughan, E. E. (2010). Novel approaches for analysing gut microbes and dietary polyphenols: challenges and opportunities. *Microbiology* **156**, 3224–3231.

Kim, D. S., Lee, E. J., Cho, K. S., Yoon, S. J., Lee, Y. H. & Hong, S. J. (2009). Preventive effects of oligomerized polyphenol on estradiol-induced prostatitis in rats. *Yonsei Med J* **50**, 391–398.

Özçelik, B., Kartal, M. & Orhan, I. (2011). Cytotoxicity, antiviral and antimicrobial activities of alkaloids, flavonoids, and phenolic acids. *Pharm Biol* **49**, 396–402.

Paolillo, R., Carratelli, C. R. & Rizzo, A. (2011). Effect of resveratrol and quercetin in experimental infection by *Salmonella enterica* serovar Typhimurium. *Int Immunopharmacol* **11**, 149–156.

Selma, M. V., Espín, J. C. & Tomás-Barberán, F. A. (2009). Interaction between phenolics and gut microbiota: role in human health. *J Agric Food Chem* **57**, 6485–6501.

Tucsek, Z., Radnai, B., Racz, B., Debreceni, B., Priber, J. K., Dolowschiak, T., Palkovics, T., Gallyas, F., Jr, Sumegi, B. & Veres, B. (2011). Suppressing LPS-induced early signal transduction in macrophages by a polyphenol degradation product: a critical role of MKP-1. *J Leukoc Biol* **89**, 105–111.