

www.pharma-mag.com

September/October 2011 ISSN 1746-174X Volume 7 Number 5

Pharma

The global magazine for the pharmaceutical and biopharmaceutical industry

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A Solution to the
Antibiotic Conundrum?

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BOTANICAL ALTERNATIVES TO ANTIBIOTIC SOLUTIONS

The world is mired into a deadly and expensive arms race. But rather than being a military endeavour, this race is of medical nature — healthcare providers versus a growing number of superbugs, and, for now, the superbugs are winning.¹

For decades, following Fleming's discovery of penicillin, scientists considered antibiotics a safe and effective method of eradicating infectious diseases. Until 20 years ago this notion may have held true; however, the world has been experiencing a resurgence of old contagions and the birth of new ones.²

The Offence

Today, methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB), vancomycin-resistant *enterococci*, cephalosporin-resistant *Neisseria gonorrhoea*, carbapenem-resistant and *Klebsiella pneumoniae*, antibiotic-resistant *Clostridium difficile* (*C. difficile*) — to name just a few — are a great source of morbidity and cause thousands of deaths every year worldwide. The Centers for Disease Control (CDC) reports that there may be as many as 500,000 cases

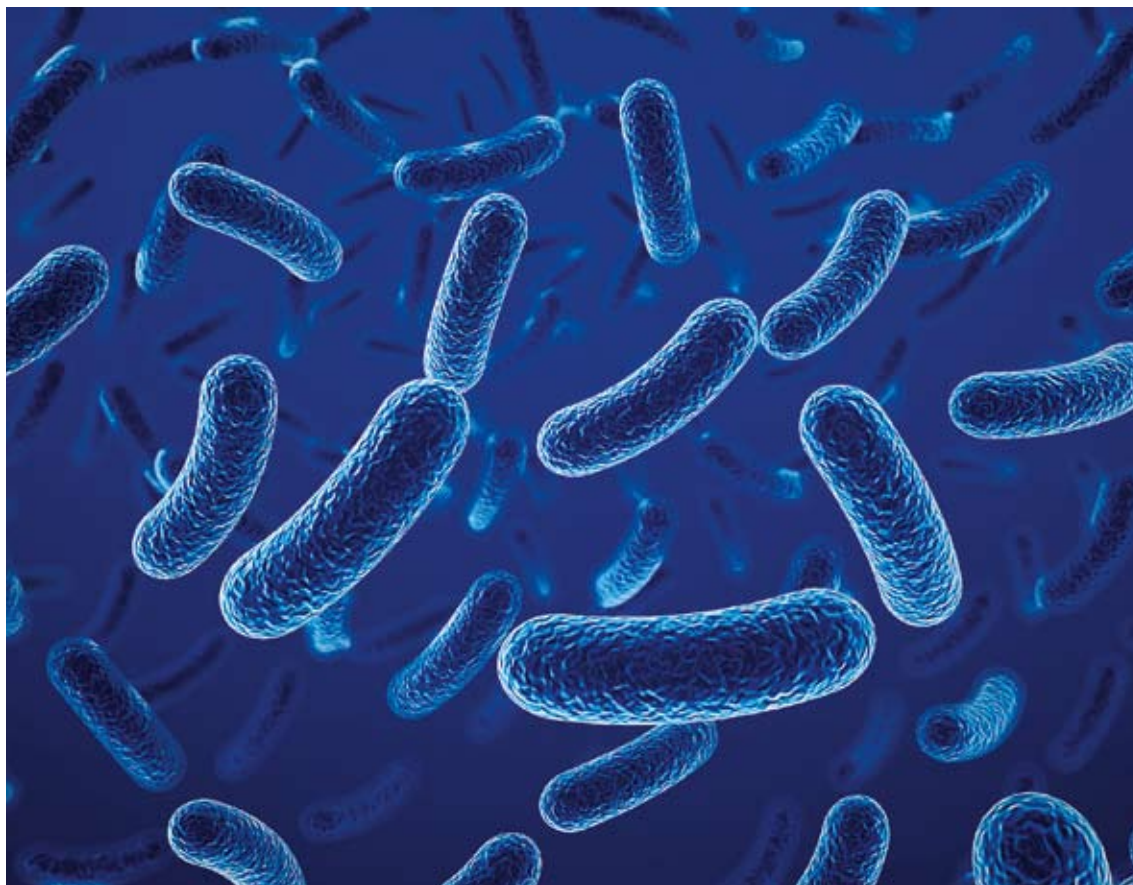
of *C. difficile* infection occurring annually in the US; up from 150,000 cases in 2001.³ With an annual death toll exceeding 15,000, *C. difficile* is now the most common cause of infectious diarrhea in US hospitals and long-term care settings.⁴ According to *Science 2.0*, MDR-TB is a growing problem in India, whereas in the US a report revealed that MDR-TB is greatly increasing the risk of contracting TB among the African-American population.^{5,6} Furthermore, the emergence of Plasmid-encoding Carbapenemase-resistant Metallo- β -Lactamase (PCM or NDM-1), an enzyme that renders bacteria resistant to a broad range of β -lactam antibiotics (including the antibiotics of the carbapenem family, the preferred treatment for antibiotic-resistant bacterial infections) has scientists worldwide calling for urgent action to stop the spread of this plasmid. Bacteria that produce carbapenemases are often referred as 'superbugs' because they cause difficult-to-treat infections.⁷

Antibiotic resistance has become such a widespread phenomenon that the US CDC has named it as "one of the world's most pressing public health problems."⁸ Writing in the *The Lancet Infectious Diseases*, Dr Tim Walsh, a leading authority in multidrug-resistant *Enterobacteriaceae* infections — which include *E. coli* and salmonella — warned that the spread of drug-resistant bacteria genes could herald the end of the antibiotics age.⁹

**HYDROXYTYROSOL
COULD EXERT
THERAPEUTIC EFFECTS
FOR THE TREATMENT
OF HUMAN
RESPIRATORY TRACT
AND INTESTINAL
INFECTIONS.**

The Paradox

'The Antibiotic Paradox' is a problem that has been created by overusing these life-saving drugs for managing conditions that could be easily addressed just by strengthening our immune system or avoiding, more absurdly, treating virus-induced illnesses, such as influenza — which is insensitive to antibiotics —



with the latest class of antibacterial remedies.¹⁰ Also, the widespread use of antimicrobial agents, such as wipes, hand-sanitizers and nebulizers, as well as the creation of antibacterial coated surfaces, including tabletops and antimicrobial tools, have compounded the problem. Whenever a chemically synthesized agent is used against micro-organisms a few of the organisms survive the application and some random mutations will produce bacteria resistance to the drug. Discontinuity of treatment — patients failing to complete their course of antibiotics — or an incorrect prophylaxis may produce a failed cure and help the emergence of a more resistant strain of the bacteria we intended to eradicate.

Drug-Resistant Bacteria Environments

And the rise of drug-resistant bacteria is not long fostered just by direct use, or misuse, of antibiotics in hospitals or for individual therapy; nowadays, bacteria mutate also in animal environments through the widespread practice of adding penicillin and tetracyclin into animal feed to improve the growth rate of healthy animals, to reduce the amount of feed used in their diet, for animal treatment during illness, and to curb recurrent infectious outbreaks caused by livestock living in cramped and unsanitary living situations. Reports by the Natural Resources Defense Council, Inc. have

found that approximately 80% of all antibiotics used in the US are utilized in animal environments to promote faster growth and less feed.¹¹

According to the Organic Consumers Association, the use of antibiotics on farms has led to an increase in antibiotic-resistant cases of campylobacter and salmonella food poisoning in humans.¹² In particular, virginiamycin-resistant bacteria — which can be found in almost 50% of supermarket-sold chicken, turkey and pork — are directly responsible for the at the least 5000 case of grave food poisoning annually. Furthermore, virginiamycin-resistant bacteria in chicken are believed to be the causative agent for the rise of synergic-resistant bacteria in humans.

The US' National Academy of Sciences claims: "The specter of untreatable infections — a regression to the prebiotic era — is looming just around the corner."¹³ In a recently published study, the Cook County Hospital (IL, USA) and the Alliance for the Prudent Use of Antibiotics reported that the use of antibiotics from all animal sources costs Americans \$16.6–26 billion annually.¹³

A New Defence Strategy

The Achilles' heel of the pharmaceutical approach to prevention and therapy for bacterial epidemics has shown its limits during Europe and America's

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latest food-borne epidemics. There is an opportunity, however, to revisit our traditional approach to antimicrobial and pathogens' control, whether it may be human diseases, food safety control and/or decontamination as in the case of an outbreak, and to expand our scientific and medical interest into natural active compounds that may provide new and more general defence against bacteria and viruses as well. Of all the natural compounds being tested in the nutraceutical and biopharmaceutical field for their antibiotic and antimicrobial properties, phytomolecules hold the greatest promise for a solution to the antibiotic paradox.

Phytomolecules, a class of plant-based biogenic substances (which includes flavonoids, carotenoids, terpenoids and polyphenols), are derived from fruit and vegetables, and are credited with having healthy and restorative properties, and for being a good source for many of the bioactives used to produce some of the newest biopharmaceuticals.

Recently, a Medical University of South Carolina's study reported that thanks to catechins (a specific class of flavanoids found in plants ranging from grape to cocoa), coffee and tea drinkers run a 50% lower risk of contracting MRSA.¹⁴ The study estimates also that, had it not been for coffee and tea catechins, the number of MRSA carriers — now standing at 2.5 million in the US — would be much higher. Processed and raw honey have been recently reported to be an effective antimicrobial agent against the proliferation of both gram-negative and gram-positive bacteria.¹⁵

Furthermore, the list of plants and plant extracts, including echinacea, goldenseal, sage, garlic, ginseng, peppermint and thyme, exhibiting (either proven or suspected) antimicrobial and antibiotic properties grows longer by the day.¹⁶ But of all the natural/novel compounds being investigated by the nutraceutical, pharma and food industries, olive polyphenols and specifically hydroxytyrosol (HT) — which have been shown to have a potent antibacterial activity against *E. coli* 107:H57, salmonella and listeria — hold the most promise.¹⁷

Hydroxytyrosol

A recent study assessed the antimicrobial effects of HT and other phenolic compounds against gram-positive and gram-negative bacteria (*Streptococcus pyogenes*, *Staphylococcus aureus* [*S. aureus*], *E. coli* and *Klebsiella pneumoniae*).¹⁸ Although the majority of the compounds tested exerted only minimal antimicrobial actions, HT induced powerful inhibition of four bacterial strains that were examined.¹⁹ One of the first complete reports of HT's potential effects against human pathogens demonstrated that this natural product exerted inhibitory actions against 49 strains of clinically relevant bacteria, including haemophilus influenzae, salmonella and *S. aureus*.²⁰ HT, at minimum inhibitory concentrations ranging from 0.24–31 µg/mL, had broad-range effects against the bacterial strains studied.²⁰ On the basis of these findings, the authors proposed that HT could exert therapeutic effects for the treatment of human respiratory tract and intestinal infections.

HT efficacy as antimicrobials applies also to its unique activity against *S. aureus*' enterotoxin A (SEA). Laboratory experiments, conducted at US Department of Agriculture in California, using Creagri Inc.'s proprietary formulation of HT with Hidrox 12%, demonstrate that the use of HT and olive polyphenols are natural, safe antimicrobials against food-borne pathogens and some of their virulent toxins, particularly Shiga toxin, produced by *E. coli* and *S. aureus* in meats, poultry and humans.²¹ Similar to *E. coli*'s toxin, SEA is a super antigen that contributes to human emesis, diarrhea, arthritis and toxic shock. Multiple evidence that HT may easily penetrate tissues and cells as a result of its unique bioavailability, together with the discovery of new processes to mass produce large, safe and effective quantities of olive polyphenols and HT for medical and industrial applications, may provide a viable alternative management to bacterial outbreak and deliver some therapeutic effects not easily obtainable with traditional synthetic antibiotics.²¹

The beneficial effect of HT and olive polyphenols on the immune system and the enhancement of the phagocytic activity of white cells/lymphocytes indicate that the benefits provided by the HT and olive polyphenols may be two fold: a direct antimicrobial activity against the pathogens and their toxins as result of its direct protein-modifying activity mechanism; the potentiating and enhancing of innate immune defence that helps the human body to fight the toxic effects of bacteria infection.^{22–24} In addition, their strong safety profile and ready availability as dietary supplements (Olivenol Plus) would justify their study as alternative natural ailment in bacteria epidemic outbreaks affecting humans. HT from olives could provide a new, more effective and substantially safer approach to health management and food safety. **Pharma**

For more information

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