

## EDITORIAL

# Are nutraceuticals the modern panacea? From myth to science

**Correspondence** Giampaolo Velo, Unit of Pharmacology, Department of Diagnostics and Public Health, University of Verona, Policlinico GB Rossi, Piazzale LA Scuro, 10, 37134 Verona, Italy. Tel.: +39 04 5802 7450; Fax: +39 04 5812 4876; E-mail: giampaolo.velo@univr.it

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Pietro Minuz<sup>1</sup>, Giampaolo Velo<sup>2,3</sup>, Francesco Violi<sup>4</sup> and Albert Ferro<sup>5</sup>

<sup>1</sup>Unit of Internal Medicine C, Department of Medicine, University of Verona, Verona, Italy, <sup>2</sup>Pharmacology Unit, Department of Diagnostics and Public Health, University of Verona, Verona, Italy, <sup>3</sup>International School of Pharmacology, Ettore Majorana Foundation and Centre for Scientific Culture, Erice, Trapani, Italy, <sup>4</sup>Clinica Medica, Atherothrombosis Centre, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy, and <sup>5</sup>Department of Clinical Pharmacology, Cardiovascular Division, British Heart Foundation Centre of Research Excellence, King's College London, London, UK

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Although it lacks the precision that is required for a scientific definition, the neologism 'nutraceutical' is evocative and somehow intuitive for those who would suggest that nutrients may have beneficial effects on health, or may promote health, so that nutraceuticals could be compared to medicines [1]. This simplistic and rather vague concept challenges the differentiation of medication from nutrient and wellbeing from health, embracing in a single term investigation of dietary habits, dietary supplements and a variety of compounds, including herbal remedies, which have been characterized in their structure and major biological effects and which may represent the 'beneficial' ingredients of certain diets or traditional medicines. As such, nutraceuticals might be seen as the contemporary equivalent of 'panacea' (Latin *panacēa*, Greek *πανάκεια*, *panakeia*, from *panakēs* 'all-healing', from *pan* 'all' + *akos* 'remedy', Oxford Dictionary), a herbal remedy dispensed to humans by Panacea, daughter of Asclepius, useful against a variety of diseases [2]; but at the same time may carry all the negative connotations (an illusory remedy) endowed in that term [1].

Being edible, nutraceuticals are often perceived as safe and are therefore freely marketed as 'fortified foods', 'functional foods' or herbal preparations. However, beyond the commercial interest, the scientific interest in this topic is expanding. The present themed issue, which is based around the course held in Erice, Sicily, at the International School of

Pharmacology of the Ettore Majorana Foundation and Centre for Scientific Culture in 2015, thanks to the support of the Menarini Foundation, summarizes some of the major issues in this largely unexplored area of medical, biological and pharmacological research, including defining the limitations of the field and depicting some important and topical lines of investigation.

## Theoretical basis

Data already exist in the field of nutraceutical research that are of considerable interest to clinical nutritionists, clinicians, pharmacologists and clinical pharmacologists. However, some points emerge as crucial in this evolving area, and these will be discussed further below. The first is the methodology that should be applied. The second is the quantification and purification of active constituents of diet and their effects in order to define any clinical effect. The third is that of potential pharmaceutical development and related regulatory considerations, as some compounds may display the characteristics of a pharmaceutical agent or may be used as a scaffold for the construction of new drugs. There are several other unresolved issues concerning nutraceuticals: the definition of acceptable levels of evidence, the identification

of protocols to be used in clinical trials testing the activity of nutrients, and the application of mechanistic and pharmacological research tools and of evidence-based medicine to herbal remedies and traditional medicines.

Concerning methodology, a comprehensive approach is required, including both clinical and pharmacological investigation. Large-scale or population-based prospective observational studies, along with small-size proof-of-concept studies, are needed for the preliminary delineation of the potential of nutrients. Properly designed randomized clinical trials, supported by rigorous basic research on chemistry, including a thorough quantification of bioavailability and bioactivity, are then required for a scientifically sound definition of biological activity and clinical efficacy of individual compounds, or of well-characterized nutrients. Mechanistic investigation associated with meticulous scrutiny for compounds of potential interest, applying an ethno-pharmacologic approach, should have a central role in this field of research [3–5]. Basic research requires an integrated approach that includes investigation of the mechanisms of disease and evaluation of appropriate and meaningful end-points [6–8]. To this aim, the use of systemic (omics) approaches with appropriate biomarkers and careful quantification of the bioavailability of the chemical entities of interest has been proposed [6]. Concerning the pharmacological applications, biotechnology offers new perspectives showing that plants may be genetically engineered to produce large amounts of drugs or vaccines that can be administered in the required amount as food, and some bioactive compounds contained in food may be used as a model on which therapeutic or diagnostic agents with increased specificity or improved bioavailability can be designed [9–11].

## Clinical evidence

These considerations are a reflection of past and ongoing research in the field. Clinical research has been largely encouraged in the past decades by epidemiological studies, indicating that specific dietary patterns, the Mediterranean diet in particular, confer cardiovascular protection beyond the contribution of appropriate caloric intake and macronutrient composition, subsequently showing that the high content of monounsaturated or polyunsaturated fatty acids or of polyphenols accounts for the observed reduction in cardiovascular events and mortality [12, 13].

The refinement of the original hypothesis has been strongly supported by progress in basic science and clinical research in the field of chronic diseases in particular: for example, the identification of oxidative stress and inflammation as major contributors to the progression of atherosclerosis, cancer, neurodegenerative disorders and inflammatory diseases, including steatohepatitis and rheumatologic disorders [8, 14]. A number of *in vitro* studies and properly designed small-size human studies using biomarkers of inflammation and vascular function as read-outs, allowed identification of a large number of nutrients, such as cocoa and olive oil, that demonstrate a close relationship between intake and biological effects, defining the relationship between intake of ‘natural’ antioxidants (polyphenols), endothelial function and

inhibition of inflammation [8, 14, 15]. The negative results of the large clinical studies with antioxidant vitamins promoted a revision of the oxidative theory of atherosclerosis and the search of mechanism-addressed treatment and prevention taking into account dietary intake of specific nutrients [16, 17]. Major prospective observational research projects are ongoing: the MOLI-SANI study, the European Prospective Investigation into Cancer and Nutrition (EPIC) study ([www.epic.iarc.fr](http://www.epic.iarc.fr)) and the Flora and Athena EU projects [18] addressing the link between diet, nutritional status, lifestyle, environmental factors and the incidence of cardiovascular disease, cancer and chronic inflammatory diseases in the studied population [18, 19]. The Predimed study ([www.predimed.es](http://www.predimed.es)), a nationwide project, is testing in a large randomized study the contribution of some nutrients that characterize the Mediterranean diet, polyphenols and omega-3 fatty acids, in primary prevention of cardiovascular events using clinical and surrogate end-points [20, 21]. Several other compounds not related to a specific dietary pattern are now under investigation, such as nitrates contained in beetroot, proteins derived from milk, conjugated linoleic acids contained in meat, lycopene and cysteine-knot proteins contained in tomatoes and other solanaceae [9, 22–24].

## Mechanistic insight

Certainly, prevention of cardiovascular disease is one pre-eminent application of nutraceuticals. This is based on the epidemiological evidence, and the results of mechanistic investigations, showing that vascular endothelium is a common target. This might also explain the pleiotropic effects, a ‘panacea-like’ activity, of nutraceuticals: dietary nitrates are converted into nitric oxide through metabolism [23, 24]; ‘natural’ antioxidant agents acting as scavengers of oxygen radical species increase nitric oxide bioavailability [15]. Enhanced nitric oxide signalling leads to vasodilatory, anti-platelet, anti-inflammatory, neuroprotective and anti-atherogenic effects [8, 25]. Modulation of oxygen radical species via inhibition of NADPH oxidase critically interrupts or activates pathways in cellular response to a variety of stimuli, as demonstrated for polyphenols contained in grapes, wine and olive oil, resulting in the disruption of pro-inflammatory signals [15]. Monounsaturated and omega-3 polyunsaturated fatty acids and conjugated linoleic acids are bioactive compounds and precursors of lipid mediators with cardiovascular effects [6]. In most studies intermediate end-points were investigated and reduction in blood pressure, improvement in endothelial function and reduction in biomarkers of inflammation and oxidative stress have been used as evidence of the bioactivity of nutraceuticals [15, 24, 25].

## Perspectives

Nutraceuticals represent neither nutrition nor pharmacology, but instead an evolving new field of research, that may generate a deeper knowledge of the mechanisms of action and the benefits that may derive from the use of evidence-based dietary patterns and the contribution of precisely identified

'nutraceuticals' or components of traditional medicine. The potential applications of nutraceuticals are therefore as multifaceted as the term itself. This may lead not only to a more logical and scientific use of nutrients, but may substantiate a nutritional approach to disease prevention and treatment [26]. Once the hypothesis of benefit has been tested and confirmatory evidence has been obtained, health authorities, from regulatory agencies to local health organizations, should take responsibility for population-addressed interventions. In some cases, innovative medications or diagnostics may be developed starting from investigations on nutrients, herbal remedies or traditional medicine, requiring a claim for their bioactivity, with definition of doses and manufacturing processes – all of which would be in line with standard pharmaceutical development [11].

In conclusion, the search for the twenty-first-century panacea is under way, but must be based on strong epidemiological data, meticulous scrutiny of compounds of potential interest, and subsequent mechanistic investigation and formal clinical research studies. Pharmacological applications may derive in some cases from biotechnology and clinical pharmacology.

## References

- 1 Aronson JK. Defining 'nutraceuticals': neither nutritious nor pharmaceutical. *Br J Clin Pharmacol* 2017; 83: 8–19.
- 2 Hippocrates, with an English translation by W. H. S. Jones. Cambridge, MA: Harvard University Press, 1957.
- 3 Layne K, Ferro A. Traditional Chinese medicines in the management of cardiovascular diseases: a comprehensive systematic review. *Br J Clin Pharmacol* 2017; 83: 20–32.
- 4 Lee SWH, Lai NM, Chaiyakunapruk N, Chong DWK. Adverse effects of herbal or dietary supplements in G6PD deficiency: a systematic review. *Br J Clin Pharmacol* 2017; 83: 172–9.
- 5 Moore N, Hamza N, Berke B, Umar A. News from Tartary: Ethnopharmacological travels on the Silk Road and elsewhere. *Br J Clin Pharmacol* 2017; 83: 33–7.
- 6 Badimon L, Vilahur G, Padro T. Systems biology approaches to understand the effects of nutrition and promote health. *Br J Clin Pharmacol* 2017; 83: 38–45.
- 7 Bruen R, Fitzsimons S, Belton O. Atheroprotective effects of conjugated linoleic acid. *Br J Clin Pharmacol* 2017; 83: 46–53.
- 8 Pantano D, Luccarini I, Nardiello P, Servili M, Stefani M, Casamenti F. Oleuropein aglycone and polyphenols from olive mill wastewater ameliorate cognitive deficits and neuropathology. *Br J Clin Pharmacol* 2017; 83: 54–62.
- 9 Molesini B, Treggiari D, Dalbeni A, Minuz P, Pandolfini T. Cystine-knot peptides: pharmacological perspectives. *Br J Clin Pharmacol* 2017; 83: 63–70.
- 10 Merlin M, Pezzotti M, Avesani L. Edible plants for oral delivery of biopharmaceuticals. *Br J Clin Pharmacol* 2017; 83: 71–81.
- 11 Drake PMW, Szeto TH, Paul MJ, Teh AY-H, Ma JKC. Recombinant biologic products versus nutraceuticals from plants – a regulatory choice? *Br J Clin Pharmacol* 2017; 83: 82–7.
- 12 Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, *et al.* The diet and 15-year death rate in the seven countries study. *Am J Epidemiol* 1986; 124: 903–15.
- 13 de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamele N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999; 99: 779–85.
- 14 Del Ben M, Polimeni L, Baratta F, Pastori D, Angelico F. The role of nutraceuticals for the treatment of non-alcoholic fatty liver disease. *Br J Clin Pharmacol* 2017; 83: 88–95.
- 15 Loffredo L, Perri L, Nocella C, Violi F. Antioxidant and antiplatelet activity by polyphenol-rich nutrients: focus on extra-virgin oil and cocoa. *Br J Clin Pharmacol* 2017; 83: 96–102.
- 16 Myung SK, Ju W, Cho B, Oh SW, Park SM, Koo BK, *et al.* Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2013; 346: f10.
- 17 Minuz P, Fava C, Cominacini L. Oxidative stress, antioxidants, and vascular damage. *Br J Clin Pharmacol* 2006; 61: 774–7.
- 18 Cerletti C, de Curtis A, Bracone F, Digesù C, Morganti AG, Iacoviello L, *et al.* Dietary anthocyanins and health: data from FLORA and ATHENA EU projects. *Br J Clin Pharmacol* 2017; 83: 103–6.
- 19 Bonaccio M, Pounis G, Cerletti C, Donati MB, Iacoviello L, de Gaetano G, *et al.* Mediterranean diet, dietary polyphenols and low-grade inflammation: results from the MOLI-SANI study. *Br J Clin Pharmacol* 2017; 83: 107–13.
- 20 Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, *et al.* Primary prevention of cardiovascular disease with a Mediterranean diet. *New Engl J Med* 2013; 368: 1279–90.
- 21 Medina-Remón A, Casas R, Tresserra-Rimbau A, Ros E, Martínez-González MA, Fitó M, *et al.* Polyphenol intake from a Mediterranean diet decreases inflammatory biomarkers related to atherosclerosis: a substudy of The PREDIMED trial. *Br J Clin Pharmacol* 2017; 83: 114–28.
- 22 Khatri J, Mills CE, Maskell P, Odongere C, Webb AJ. It is rocket science: Why dietary nitrate is hard to beet! Part I: Twists and turns in the realisation of the nitrate-nitrite-NO pathway. *Br J Clin Pharmacol* 2017; 83: 129–39.
- 23 Mills CE, Khatri J, Maskell P, Odongere C, Webb AJ. It is rocket science: Why dietary nitrate is hard to beet! Part II: Further mechanisms and therapeutic potential of the nitrate-nitrite-NO pathway. *Br J Clin Pharmacol* 2017; 83: 140–51.
- 24 Marcone S, Belton O, Fitzgerald DJ. Milk-derived bioactive peptides and their health promoting effects: a potential role in atherosclerosis. *Br J Clin Pharmacol* 2017; 83: 152–62.
- 25 Borghi C, Cicero AFG. Nutraceuticals with clinically detectable blood pressure lowering effect: a review of available randomized clinical trials and their meta-analyses. *Br J Clin Pharmacol* 2017; 83: 163–71.
- 26 Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, *et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016; 37: 2315–81.