Editorial

Nutraceuticals: is there good science behind the hype?

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The term 'nutraceuticals' was originally coined in the late 1980s [1] and has since been used to describe a wide variety of non-pharmaceutical compounds that may have an impact on health and disease states, general well-being and performance. The term is poorly defined and has been used by consumers, producers and even healthcare professionals to refer to many different types of compounds, including (semi-)purified substances from natural sources, plant extracts, dietary supplements, vitamins and minerals, phytonutrients, various products with combinations of functional ingredients and even (modified) whole foods. One of the issues that has beset the field is that good science in this area has frequently been misinterpreted or overstretched for commercial purposes. Nevertheless, the border ground between nutrition and pharmacology is clearly a fertile ground for clinical pharmacology and therapeutics, where rigorous science is absolutely vital. A very old example is the introduction of high dose oral folate therapy as an alternative to vitamin B12 in treating pernicious anaemia in the 1930s, which certainly did not halt progression of subacute combined degeneration of the cord and may have accelerated it. An issue that is still unresolved and reflected in divergent public health policy is the fortification of flour with folate, done in the USA with probable benefit in terms of reduced neonatal neural tube defects, but not in the UK because of the theoretical concern as to possible unmasking of subacute combined degeneration of the cord in people with borderline unrecognized vitamin B12 deficiency.

It is also clear that there is a high level of interest, and consequently a high consumer demand, for nutraceutical-type products by the general public. Such products are often perceived in a more favourable light than pharmaceuticals, being seen as more 'natural' and less likely to cause side effects (which is often far from true, see e.g. [2, 3]). They are also generally easier to obtain, being available over the counter in supermarkets, health food shops and pharmacies, and have not always been subject to the

same level of regulatory scrutiny before reaching the marketplace. In the past years, rigorous regulatory assessments for the approval of health claims, such as carried out by the EFSA (European Food Safety Authority) under the European Union health claims legislation [4], have been implemented. These are designed to protect the consumer from misleading product communication, and create a powerful research drive to substantiate nutraceutical effects according to the strictest scientific criteria. Good science is already carried out in many areas, and this is the focus of the current issue of the *British Journal of Clinical Pharmacology*.

The scope of the nutraceutical field is enormous, both in terms of types of interventions and the variety of health outcomes. Conceptually, the area can be seen as positioned between medicinal drugs and basic nutrition, with approaches and products on the far ends of the spectrum either emphasizing the '-ceutical' (i.e. resembling pharmaceuticals approaches) or the 'nutri-' (i.e. towards basic nutritional concepts) parts of the word 'nutraceuticals'. On one side there are products that are exclusively or primarily consumed for their functional effects. These products often find their roots in traditional medicine, such as many herbal compounds [5], and are often marketed and consumed in ways that emulate aspects of mainstream pharmaceuticals, as capsules or liquid formulations, often with specific dosing regimens. On the opposite side lies an approach that is rooted in nutritional science. Here the focus is on optimizing or fine-tuning normal dietary components to provide the best health or functional outcomes. Typically the products revolve around the levels of micronutrients (vitamins, minerals) and macronutrients (proteins, lipids, carbohydrates) that need to be consumed in order to alleviate or prevent deficiencies or overconsumption, as well as improving the quality of particularly macronutrients to exert certain health benefits. Examples of this approach are supplementation or fortification products with vitamins and minerals, 'light' products

with less sugar or fat, alternative energy sources [6], claims related to the health impact of lipids from different omega families [7] and rapidly vs. slowly available carbohydrates. Increasingly, research activities are focussing on the identification and substantiation of novel actions and health benefits of mainstream nutritional components, such as polyphenols [8, 9] or dietary nitrate [10]. Alternatively, previously conceived concepts such as the health impact of dietary anti-oxidants are challenged and redefined [11]. Nutritional approaches are often initially inspired by epidemiological findings and the products typically are modified versions of traditional food products. Throughout the nutraceutical spectrum many product variations and crossovers exist: nutritional solutions are leveraged in a 'pharmaceutical' way (e.g. fish oil capsules or vitamin supplements) and functional ingredients are incorporated in 'nutritional' food items (e.g. probiotics [12], plant sterols).

Regardless of product type, commercial positioning and health benefit area, the functional claims of any nutraceutical product should be evidence-based and supported by convincing scientific data. Ultimately, the proof of efficacy, as well as of safety, should come from well-designed and well-executed human studies. Although the basic methodology of designing and conducting human studies on the health benefits of nutraceuticals [13] is similar to that of pharmaceutical trials, there are aspects that need special consideration when investigating nutraceuticals. For example, since nutraceuticals are often taken as 'self-medication', the target population, and hence the study population, may not necessarily be well characterized, and population heterogeneity may lead to variability in the observed effects. Additional variability may occur if non-disease-related or noisy outcome measures are used. The properties of the nutraceutical compound itself may also modulate study results in a non-straightforward fashion. Particularly when influences related to more substantial dietary modifications are investigated, newly introduced food components often are not added to the diet but replace foods usually consumed. Any effect may therefore be either attributable to the newly introduced product, the removal of the previous product or a combination of the two. As discussed in [14], disentangling and optimizing the bioavailability and kinetic profiles of nutraceutical and nutritional compounds poses some specific challenges. Furthermore, especially when dealing with complex mixtures derived from herbal plants, the exact bioactive fractions or compound(s) are not easily characterized, leading to issues in controlling the intake of such bioactives, particularly with natural variation in the plant composition. The notion that different bioactives within a particular nutraceutical or within a diet may exert (unknown) antagonistic, agonistic or synergistic effects further complicates the interpretation of any research findings. Other interaction effects may arise when nutraceutical approaches are placed in a broader lifestyle context, a concept that is gaining much interest recently. Breen &

Philipps [15], for example, discuss the interaction between protein intake and resistance-type exercise to maintain muscle mass. Another example is the notion that nutrition together with other lifestyle interventions may be effective in preventing neurodegenerative diseases [16]. Lastly, the majority of nutraceutical interventions are thought to exert their positive health effects after long term exposure, i.e. months to years, and sometimes even decades. This notion introduces serious methodological challenges for designing human intervention trials, particularly in the absence of validated diagnostics, risk factor or early efficacy markers (see, e.g. [17, 18]).

On the other hand, some of the above characteristics of the nutraceutical approach are also claimed to give a conceptual advantage over the traditional pharmaceutical approach. Complex mixtures or diets may target multiple physiological mechanisms simultaneously in a milder fashion, leading to a more sustainable and more integrated approach to improving health.

The current issue provides a selection of overview articles that represent some key concepts, findings and directions in the nutraceutical field. They not only illustrate that significant scientific advancements have been made in the field, but also highlight that an evidence-based nutraceutical approach can make important contributions to public health, in addition to, not instead of, pharmaceutical therapies.

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