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Nutraceuticals: Health Benefits and Government Regulations

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In 1989 Stephen DeFelice coined the term "nutraceuticals", defining it as "food or part of a food that provides medical or health benefits, including the prevention and/or treatment of a disease".[1] Therefore, nutraceuticals are vegetable or animal food deriving molecules which help in the prevention and assist the treatment of human disease. Their effects on human health go beyond nutrition and can be displayed by including these substances in the daily diet and/or by using food supplements.

Today, the regulatory definition of this term has not yet been finalised; therefore, nutraceutical based-products, available in the market and drugstore without any prescription, can be considered food, herbal products or food supplement and the existing contradictory information about them generates confusion about their effective use. If they are considered food supplement, in order to claim their specific beneficial effects for pathologic conditions, an European Food Safety Agency (EFSA) positive opinion is required in Europe; this imply the need to demonstrate a clear cause-effect relationship substantiated by clinical studies on healthy people.[2] Nutraceuticals generally have good safety profile and only few unwanted side effects are known.[3] In any case, risk analysis should be considered and when a possible side effect is identified, but not fully substantiated, a precaution should be taken to reduce the risk of affecting human and animal health, plants, and also the environment. In Europe, after positive EFSA opinion, each Member State can decide to set specific authorization for the registration of product before its producing and selling.[2] In USA, conversely, the manufacturer is responsible for nutraceutical safety and neither FDA approval nor registration of the products are needed before the sale. Governmental agencies only provide a surveillance activity.4 In Canada regulation is more stringent, as nutraceuticals are considered quite similar to drugs.[5] In some countries of South America a simple registration of the products is required, while in other countries animal or human clinical studies are necessary before the registration to substantiate the efficacy and safety of the claimed effect.[6] In Australia, nutraceuticals are regulated as a food category.[7] In Japan, the first country to regulate food supplements by issuing Foods for Specified Health Use (FOSHU),[8] even if a health beneficial activity is not validated with scientific evidence, but the ingredient meets safety requirements of FOSHU, it can be approved.[9]

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Today many published researches discuss the use of nutraceuticals for their different health promoting or disease preventing effects.

In the last ten years, an increased numbers of relevant clinical data regarding the effects of polyphenols, vitamins, ω-3 polyunsaturated fatty acids, fiber, minerals, and other nutraceuticals have been published.

Polyphenols are a class of compounds in which at least one aromatic ring with hydroxyl groups linked is present. This basic structure can be differently saturated, alkylated and glycosylated giving rise to non-flavonoids and flavonoids substances; these last ones can be again subdivided in flavones, flavanones, flavonols, flavanols, isoflavones, and anthocyanidins. Polyphenols have mainly healthy effects on neurocognitive performance and neurodegerative pathologies by acting as antioxidants with different mechanisms of action (Reactive Oxygen Substances-ROS scavengers, transition metal chelators, antioxidant enzyme activators). Moreover, they can also act by reducing neuronal damage caused by inflammation and neurotoxins and by interacting with intracellular and extracellular molecular signalling cascades.[10-12] However, when tested in humans, these molecules generally failed as demonstrated by the results of clinical trials. In fact, they are not so able to cross the blood-brain barrier and thus new strategies are needed to improve their bioavailability at brain level. More recently, for example, curcumin conjugated with polymers of the surface of gold nanoparticles interacted more efficiently with amyloid peptide.[13] Another successfully application that improved the low water solubility of curcumin, was the creation of nanoliposomes conjugating curcumin. This new delivery system promotes a suitable planar structure for interaction with amyloid peptides was set up, thus leading to the possibility of use this conjugate both in the diagnosis and in targeted drug delivery in patients with Alzheimer's disease.[14] ω-3 polyunsaturated fatty acids (PUFA) improved mild cognitive-impairment and, in part, specific outcomes in Alzheimer's disease.[15-16]

A high number of studies have also addressed the potential role of polyphenols in the prevention of different type of cancers. For example, the consumption of soy isoflavone indicated a lower prostate cancer incidence in elderly men than in younger men, as well as green tea catechins supplementation indicated a reduction of incidence in men with high-grade prostate intraepithelial neoplasia.[17-18] Following some epidemiological studies, which pointed out that population with high intake of certain foods and beverages had lower incidence of gastro-intestinal cancers, many researches on animal models of carcinogenesis have been performed. These studies indicated that carotenoids, stilbenes, catechins, fiber, and other food components may have a great significance in the chemoprevention of this types of neoplasia.[19] Moreover, some clinical trials have also indicated the protective role of polyphenols in colorectal cancer.[20]

Today, nutraceuticals are recognized for their positive effects in inflammatory bowel diseases, even if these healthy activities (in antioxidant defence systems, cell proliferation, gene expression, modulation of the immune response, and control of the different pathways of inflammation) have been mainly demonstrated in in vitro and animal tests and only few clinical trials have been performed.[21]

In the last two decades, the use of nutraceuticals in the management of hypercholesterolemia increased. In particular mannans, β-glucans, glucomammans, plant sterols, alkaloids (such as berberine), curcuminoids, policosanol, and many different associations of the before cited components have been used as hypolipidemic agents by acting at the different key step of the lipid metabolism.[22]

Despite the high number of nutraceuticals tested *in vitro* and animal model tests, only a few number of human clinical trials have been conducted and only stanols, sterols, ω-3 PUFAs, Chinese red yeast extract have been approved by EFSA and/or FDA for their consolidated effects against cardiovascular diseases, and calcium and vitamin D for the treatment of osteoporosis.[23]

In many cases, nutraceuticals are very complex matrices and therefore it is difficult to attribute the registered bioactivity to only one component. Therefore, it is necessary to better characterize the chemical composition (quali- and quantitavie profiles) of the matrix. Moreover, many interactions between nutraceuticals and food and/or drugs, and microbiota may occur, thus influencing bioaccessibility, adsorption, distribution, metabolism, and excretion of all components present in the nutraceutical matrix. Generally, being considered of food-origin, nutraceuticals are considered safe, but in some case many inconsistent results have been published and therefore well-designed studies, including the toxicological evaluation in pre-clinical studies, are needed to confirm their safety.

In conclusion, considered all the above mentioned, only a little number of nutraceuticals can be certainly useful for the prevention and/or treatment of diseases. Many published reviews, summarizing the state of art of the different class of nutraceuticals, are present in literature and can stimulate the interest of the reader. Nutraceutical are very promising components of our diet, as demonstrated by the high number of in vitro and pre-clinical studies; but, today the lack of well conducted trials is a crucial key point. Only overcoming this "*rock*" and including nutraceuticals in the Regulations by defining a new category of products we may have the possibility to take a step forward.

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