

Nutraceuticals and Mediterranean Diet

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In recent years, the chemistry research of natural products has focused on the identification of biologically active secondary metabolites in plants, commonly used as vegetables in the human diet and which, in past centuries, had been used not only as food or spices but also in traditional medicinal remedies. The main contribution that can be attributed to plants is the introduction for example of vitamins or minerals to the human diet. However, they contain other secondary metabolites, which are defined as nutraceuticals and which have recently been, at the center of large scientific studies. Edible plants are rich in polyphenols [1], terpenoids [2-4], flavonoids, alkaloids, sterols, pigments and unsaturated fatty acids, which play an important role in maintaining wellness. The Mediterranean diet includes a good amount of plant food (fruits, vegetables, nuts, seeds, wine, olive oil) [5], which by preventing oxidation reactions, results in a significant reduction of risk factors in coronary heart disease and in lowering cholesterol levels in blood [6]. They also result in the decrease in the risk of chronic degenerative diseases such as cancer, Alzheimer's, Parkinson's disease, autoimmune diseases and multiple sclerosis [7,8]. Epidemiological studies have attributed these positive effects to the presence of compounds having antioxidant activity in foods (and beverages) commonly known as polyphenols. From the chemical point of view the polyphenols are classified into two groups: flavonoids and non-flavonoids. Belonging to the flavonoids group, flavonols present themselves both in free form or as glycosides; the flavan-3-ols such as catechin, and anthocyanins such as malvidin-3-glycoside. Among the non-flavonoids there is gallic acid, the hydroxycinnamate such as *p*-coumaric acid, caffeic acid [9] and the caftaric acid and stilbenes such as *trans*- and *cis*-resveratrol. The most significant component of the polyphenols is made up of condensed tannins, also known as procyanidins. They are oligomers and polymers of catechins (catechin or epicatechin), condensed by 4-6 and 4-8 carbon-carbon bonds. Grapes contain catechins and procyanidins in the seeds and skins and are major constituents of red wine, along with resveratrol; epigallocatechin is abundant in green tea [8-10]. The interest for the antioxidant compounds derives from the observation of their role in modulating the production of free radicals. A very timely topic in research on the pathogenesis of many diseases is related to the role played by the uncontrolled formation of free radicals: the action of free radicals as mediators of tissue damage is in fact recognized in many pathophysiological processes such as inflammation, atherosclerosis, ischemia, tumors, the damage induced by ionizing radiation, aging and skin photoreaction.

Currently, the majority of Italian medicinal plant species are harvested in the wild. This exploitation, in addition to the replacement of old local varieties with highly productive modern varieties over time, can lead to a rapid process of simplification, reducing the biodiversity of ecosystems. The *in vitro* propagation of the aromatic and medicinal species represents a great potential for the conservation *ex-situ* of ecotypes with particular characteristics [11] and for the large scale production of bioactive molecules [12]. Among these some are already being used either as herbs, both for the extraction of essential oils and aromatic compounds for use in herbal medicine and pharmacology. Many scientific publications have attributed to the plant extracts used as food or spice such as *Capsicum annuum* L. (Pepper) in sweet or spicy forms [13,14], and plants belonging to the family Liliaceae such as

garlic (*A. sativum* L.), onion (*A. cepa* L.), leek (*A. porrum* L.), shallot (*A. ascalonicum* L.) [15] interesting pharmacological activities, including antimicrobial, anticancer and anti-platelet aggregation. Recent studies have led to the identification of numerous organic compounds whose structure has been determined predominantly by spectroscopic non-destructive methods (NMR mono- and two-dimensional experiments), techniques to preserve the natural product and then by carrying out pharmacological investigation. From the seeds of various species of *Allium* and *Capsicum* new cytotoxic saponins and sapogenins with antimicrobial activity were isolated [16] as well as a large number of glycosides and phenolic derivatives of various kinds, on some of them tests were made to evaluate the antiplatelet and antioxidant action [13]. The Lamiaceae, of which some of the species was used in folk medicine, in cosmetics and nutrition for centuries, are a family of plants widely distributed in all temperate zones. In the Mediterranean about thirty types were recorded and it was observed that there is a large intraspecific variation. It would therefore be desirable to add to the morphological description of each species a fingerprint of secondary metabolites or at least the quantitative determination of the more biologically active compounds. As it is well known, the secondary metabolites may be subject to considerable variations in a living plant as a function of environmental and ontogenetic factors [17]. Rosemary [18], sage [19], winter savory [20], basil [21], mint [22], oregano [23] and thymus [24] have been studied extensively for their antioxidant properties, while this biological activity has not been tested at all for other kinds.

Nutraceutical is a "portmanteau" word, a combination from the two words "nutrition" and "pharmaceutical" and refers to the study of foods that have beneficial effects on human health. The term was coined by Dr. Stephen DeFelice in 1989. Nutraceutical foods are described as "functional foods", "pharma foods" or "farmalimenti". A nutraceutical is a "food-drug" or a health food that associated with nutritional components selected for characteristics such as digestibility and hypoallergenic and the healing properties of natural active ingredients extracted from plants, has a proven and recognized efficacy. Reliable sources estimate the turnover in the United States in 1997 to be about \$35 billion dollars spent on these products. An increase of 2.7% is estimated per year. In Europe it is estimated that currently the revenue from products alone is €5 billion per year and €500 million euro per year in Italy. It is believed that these data are underestimated, because the use of nutraceuticals is second in order of importance to alternative therapy and is used by about 40% of patients. Nutraceutical is therefore the science that deals with the study of those foods, or parts of those foods that have particular beneficial, preventative and therapeutic effects on human health. Very often the word nutraceutical is compared

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to the adjective 'functional' even if a functional food is not necessarily said to be a nutraceutical food. A food is therefore considered to be functional when it is used as for its ability to prevent or treat specific diseases, such as is the case with fruit and vegetables consumed to prevent certain diseases and/or forms of cancer, while a nutraceutical is nothing more than a preparation of pharmaceuticals (pills, capsules, etc..) containing the active ingredients found in functional foods, but extracted, purified, concentrated and assayed. Decaffeinated green tea can be used as a simple example, it is considered as a functional food if the daily intake is about 10-12 cups and it has shown to be able to prevent some degenerative diseases including certain types of cancer [25], but it is also true that it is used as a basis for certain nutraceutical products containing catechins that have in turn been extracted from it [26]. Catechins are flavonoids found in chocolate, fruits, vegetables, wine and many other plant species. The importance of catechins has been demonstrated more than once in the literature and in particular the basic role of inhibitor of the proliferation of cancer cells, in the reduction of atherosclerotic plaques, in the prevention of cardiovascular diseases, and in addition they have an important antioxidant action and regulate the cellular cycle. In addition to having a direct anti-oxidant action, catechins strengthen other antioxidant systems, such as those in which vitamin E is involved. Recent research has also shown additional health benefits, thanks to their hepatoprotective, immunostimulant properties and the favorable effects they have on blood circulation and blood pressure. It has been known since antiquity that nature is an inexhaustible source of plants with phytotherapeutic, nutritional, and functional properties and now with nutraceuticals a similar argument can be made for another food: carob, a leguminous evergreen cultivated in Mediterranean regions. This plant is used both as a functional food and as a nutraceutical because from its leaves, seeds and fruits galactomannans, catechins, hydrolysable tannins and benzodiazepin-like substances etc. can be extracted. Even if its reputation in the food industry is mainly for flour made from its seeds, known to be a flour with a high hydrocolloid property (absorbs up to 40% water) due to the presence of carrubine and seldom if ever is it used or considered as a true functional food for its prebiotic action fibres [27]. The list is very long. Can we consider this a great advancement in the pharmaceutical/nutritional sector, or an innovative futuristic conception of food and the first step towards food pills?

Among food-related nutraceuticals other than yogurt, there are above all the fruit and vegetables rich in antioxidants. Leutine, useful for sight, is found in spinach, kale, broccoli and eggs [28]. Curcumin the yellow pigment is found in curry and saffron. We have isoflavones in legumes. Yeast contains amino acids, carbohydrates, proteins, minerals and vitamins. Pycnogenol from the bark of the maritime pine is useful for the prevention of cardiovascular diseases and dermatological complaints. From grape skin and the famous win polyphenols resveratrol is extracted and used [9]. In tea there is theanine and theine. As for the polyphenols, carotenoids, folic acid, vitamins, minerals, melatonin, carnitine and Omega3 are all well known. The Mediterranean diet includes: a daily intake of fruit, vegetables, milk, dairy products, olive oil, complex carbohydrates, a weekly intake of white meat and fish, and an occasional intake of red meat and sweet foods. It was therefore attempted to reproduce in pill form the active ingredients found in the Mediterranean diet. But, as a general rule, the natural substances consumed as fresh food or fresh extracts are always more active than other preparations because of the absence of deterioration due to processing, and greater intestinal absorbability. For decades nutritional recommendations of various national and supranational organisms were more focused on "what not to eat"

without prejudicing an adequate intake of essential nutrients such as amino acids and essential fatty acids, vitamins, minerals and water. It was recommended to limit the intake of substances such as saturated fatty acids, cholesterol and sodium.

Scientists now recognize that the other aspect of nutrition, that is "what to eat," can be just as important or even more important. It is believed that people who follow a diet rich in natural foods such as fruit, vegetables, nuts, whole grain and fish, tend to have a lower risk of disease. The incidence of certain cancers and cardiovascular diseases is significantly lower than in populations where the consumption of these foods is lower. For a long time, some nutritionists believed that these observations were more of a random combination than a cause-effect relationship. In other words, the highest incidence of disease is the result of a high intake of meat, having a larger body fat index and a low level of physical activity, associated with a low consumption of fruit and vegetables for example, rather than the lack of these foods. Thus, the recommendations were focused on limiting the number of certain 'bad' foods and replacing them with food not-associated with degenerative diseases, and considered "good" rather than unhealthy. Over time and with the progress of analytical methods, the composition of 'good' foods has been better defined and it was soon realized that many natural foods can be used both for prevention and as an adjuvant therapy for specific diseases. Today we think that actually there is a closer link between man and nature. This provides us not only the essential components of the diet but also specific factors that protect us from the environment in which we live and the potentially pathological situations that we develop within us. Nutrients were, as is the case for animals and plants from which we derive these foods, an environmental instrument used to model the human genome. And therefore logical to assume that eating more raw foods such as fruits and vegetables, would lead to a healthier life. Technological progress has allowed us not only to understand better the characteristics of the diet we eat, but has also opened the door to an interesting commercial enterprise. Food manufacturers are now able to market foods that defend the right to good health, ensuring the nutraceutical properties themselves, they are also capable of "enhancing" nutraceutical foods by using existing substances and/or create new foods designed to include one or more nutraceutical substances in their preparations. The opportunities for the food industry involved in the production of functional foods, would seem to be unlimited.

In recent years, the concept of food has undergone a radical transformation to the extent that food is not only attributed with nutritional and sensory properties but it also has an important role in good health maintenance, psycho-physical well-being and the prevention of certain diseases. Surely there are various factors that have contributed to this development of this new interpretation of nutrition and certainly an important contribution is derived from the many scientific studies that have shown in the last decade, with plenty of experimental data, the close link that exists between nutrition and health. Functional foods are tangible evidence of this historic transformation that is occurring around food. Despite the different interpretations as to their identity, to functional food is required to have a beneficial effect on human health, maintaining a state of wellness or to be able to prevent the onset of certain diseases. Recently, several pieces of work have appeared in the literature that highlights not only the importance of the food matrix but also the production process on the bioavailability of the active components of functional foods. Unfortunately in the literature there is still little experimental work done, related to the bioavailability of active ingredients of functional foods. Furthermore, the strong influence of the food matrix on the

gastrointestinal absorption of active substances, and therefore on their bioavailability, does not allow the use of the numerous data in the literature and data relating to certain biological activities *in vitro* for the individual components of a functional food. In fact, although being active *in vitro*, they may not exert any beneficial effect when administered *in vivo* due to their poor bioavailability potential. In the case in which the “claim” a functional food makes with regards to the capacity to prevent a given disease, eg. biophenols and the preventative effect of red wine [9] against cardiovascular disease. Here the health potential will be highlighted or be shown by epidemiological studies (long and costly) or by demonstrating the inhibition of a biological process that is expected to contribute to the onset of the disease, eg. the inhibition of the oxidation of LDL in order to demonstrate the protective effect against cardiovascular disorders. Different is the case of products derived from food, which are able to enhance the body's defenses against a given disease to the point that the positive effects of their supplementation may be easily and immediately experienced by those who use them. Recently, for example, a dietary supplement (Anallergy) has been introduced into pharmacies. It contains an extract from a variety of *Pantelleria caper* (*Capparis spinosa*) [29] which, together with other extracts from the food matrix, is able to power the body to the point that it is able to counteract the harmful effects caused by allergens in allergic subjects. In this case the effectiveness of the product can be highlighted by the same allergic subjects who, in taking the product, are able to evaluate the benefits with immediacy in respect to the symptoms triggered off by exposure to allergens. In light of the above mentioned, it is clear that the development of functional foods will depend greatly on the scientific literature that will be necessary to give more scientific value and authority to what these products are capable of, which in our opinion is to have an important role in health management and human welfare.

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