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Nutraceuticals: a piece of history, present status and outlook

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Abstract

The term ''nutraceutical'' was coined in 1989 by the Foundation for Innovation in Medicine (New York, US), to provide a name for this rapidly growing area of biomedical research. A nutraceutical was defined as any substance that may be considered a food or part of a food and provides medical or health benefits including the prevention and treatment of disease. Nutraceuticals may range from isolated nutrients, dietary supplements and diets to genetically engineered ''designer'' foods, herbal products and processed products such as cereals, soups and beverages. Doubtlessly, many of these products possess pertinent physiological functions and valuable biological activities. The ongoing research will lead to a new generation of foods, which will certainly cause the interface between food and drug to become increasingly permeable. The present accumulated knowledge about nutraceuticals represents undoubtedly a great challenge for nutritionists, physicians, food technologists and food chemists. Public health authorities consider prevention and treatment with nutraceuticals as a powerful instrument in maintaining health and to act against nutritionally induced acute and chronic diseases, thereby promoting optimal health, longevity and quality of life.

Keywords: Nutraceuticals; Functional food; Phytochemicals; Designer food

1. A piece of history

> The scientist to be successful must be a sort of Janus looking at the same time to the future and the past—Francisco Grande

Throughout history, civilized societies have devoted a deep interest in, and concern about, the integrity of food supply. Long before the development of the distinct scientific discipline of nutrition, philosophers and later physicians paid close attention to the role of the daily diet in individual and public health. Interestingly, during the last 2000 years, from the time of Hippokrates (460–377 BC) to the dawn of modern medicine, there was little distinction made between food and drugs. The practice of medicine itself consisted largely of the wise choice of natural food products.

Hippokrates clearly recognized the essential relationship between food and health and emphasized that ''...differences of diseases depend on nutriment'' (Jones, 1923a, 1923b). Pliny the Elder (23–79 AD) found widespread adulteration throughout food and drug supply outlined in his Natural History ''...so many poisons are employed to force wine to suit our taste—and we are surprised that it is not wholesome''. Pliny also reflected the layperson's distrust of medical practice that has existed throughout the ages: ''Physicians acquire their knowledge from our danger by considering poisons as...food constituents in our daily nutrition, though the greatest aid to health is moderation in food. Only a physician can commit homicide with complete impunity'' (Rackham, 1949). In contrast, Galen (131–201 AD), a physician, reflected confidence in the knowledge and ability of physicians to establish sound diets that would advance public health (Green, 1951).

Overstated beliefs in the effects of aliments upon health and disease, appear to be based on magical thinking about food. Utilizing the primeval principle that like makes like, the alchemists pursued their search for the ''elixir vitae''. Modern successors of the alchemists employed the same concept. Casimir Funk discovered in the shell of rice grain a nitrogen-containing amine-base (amine); since he thought that this substance is ''life-essential'' for the human being, he defined the idiom ''Vitamin'' from ''Vita = life'' and ''amine''

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(Funk, 1912). He also reviewed evidence concerning the etiology of several food-related diseases and proposed that the absence of "vitamins" caused those diseases. Indeed, it is fascinating that the power we today attribute to vitamins is not unlike that one described to "elixir vitae" (Bitensky, 1973).

2. What are nutraceuticals?

The term "nutraceutical" was coined in 1989 by the Foundation for Innovation in Medicine (New York, US; an educational foundation established in the US to encourage discoveries in medicine), to provide a name for this rapidly growing area of biomedical research. A nutraceutical can be defined as any substance that may be considered a food or part of a food and provides medical or health benefits including the prevention and treatment of disease (DeFelice, 1992). Nutraceuticals may range from isolated nutrients, dietary supplements and diets to genetically engineered "designer" foods, herbal products and processed products such as cereals, soups and beverages. Selected nutritive nutraceuticals are listed in Table 1.

Doubtlessly, many of these substances possess important physiological functions and valuable biological activities, which certainly do not need to be described in detail. Nevertheless, some consideration of certain major and actual nutraceuticals is pertinent.

An actual class of nutraceuticals is represented by the polyunsaturated fatty acids (PUFAs) especially by those of the n-3 and n-6 fatty acid (FA) families. Current interest is devoted to the so-called fish-oils containing a high share of n-3 FA [eicosapentaenoic (EPA) and docosahexaenoic acids (DHA)]. It is claimed that these particular FA exert a protective effect on the development of cardiovascular and inflammatory diseases and the beneficial effects of fish oil supplementation in many other chronic diseases have been advocated. Many recent observations suggest a potential role for fish oils in the treatment of atopic dermatitis and psoriasis. Dietary n-3 FA treatment offers exciting novel possibilities in malignant diseases. There are also indications that premature infants have limited dietary support of the n-3 FA required for the normal composition of brain and retinal lipids (for references c.f. Fürst & Kuhn, 2000).

Treatment of cancer cachexia with fish oils might be a highly interesting future application. Fish oils probably inhibit end-organ effects of tumor-derived lipolytic and proteolytic factors, thereby influencing the activity of a number of receptors and enzymes which have a fundamental role in cellular signaling. Other possible mechanisms include interaction with peroxisome proliferator activated receptor-a (PPARa) which is a gene transcription factor that induces the breakdown of leukotrienes and thus has a role in limiting the duration and extent of inflammation (for references c.f. Fürst & Kuhn, 2000). In clinical setting, daily administration of 6 g EPA in 27 patients with pancreatic cancer caused a reversal of weight loss which persisted 3 months. Weight gain was associated with decreases of anti-inflammatory factors like CRP, IL-6 and TNF-α (Fig. 1; (Ross, Moses, & Fearon, 1999; Wigmore, Fearon, Maingay, & Ross, 1997; Wigmore et al. 1996).

The essential question of which is the most advantageous n-3/n-6 FA ratio should be raised. For nearly 2 million years our prehistoric ancestor probably consumed paleolithic nutrition with equal mix of n-3 and n-6 FA like the current Inuit or Alaskan diet (Eaton & Konner, 1985). In clinical setting, an n-3:6 FA ratio of 1:2 was proposed to achieve the most favorable modulation of lipid mediator synthesis (Morlion, Torwesten, Wrenger, Puchstein, & Fürst, 1997). This hypothesis is in good agreement with the current consensus, which was reached on the importance of reducing the share of n-6 FA, even as n-3 FA are slowly increasing in the diet of adults and new-borns. This measure is mandatory for optimal brain and cardiovascular health and function. Simultaneously, it was recommended by a working group as organized by NIH (7–9 April 1999, Bethesda, USA) that the majority of FA should be obtained from monounsaturated FA (Simopoulos, Leaf, & Salem, 1999). Accordingly, we recently had the opportunity to study in vivo the metabolism of a new type of emulsion made of a mixture of soybean long chain triglycerides (LCT), middle chain triglycerides (MCT), olive oil and

Table 1
Selected nutritive nutraceuticals

Dietary fiber
Polyunsaturated fatty acids (PUFA, fish oil)
Proteins, peptides, amino aids, keto acids
Minerals
Antioxidative vitamins
Other antioxidants (glutathione, selen, etc.)

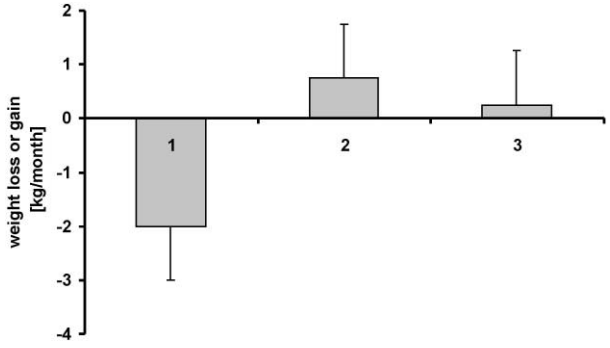

Fig. 1. The effect of PUFAs (6 g eicosapentaenoic acid C20:5 n-3, for 4 weeks) on the progress of cachexia in 27 patients with pancreatic cancer. (1) Before supplementation, (2) after 4 weeks, (3) after 3 months (modified from Wigmore, et al., 1996).

fish oil triglycerides (SMOF), supplemented with excess vitamin E. We hypothesized that this new emulsion with reduced content of n-6 FA, high share of monounsaturated FA and increased amount of n-3 FA might exert beneficial (immunomodulatory) effects. In double blind randomized studies in traumatized patients with SMOF we found considerably increased concentrations of EPA and DHA enhanced ratio of EPA/arachidonic acid (AA) and augmented releases of CTB_5 while that of CTB_4 was reduced. Most importantly the length of hospitalization was reduced with SMOF by 7 days compared with conventional long chain fatty acid based emulsion. We conclude that treatment with SMOF is well tolerated and modulates fatty acid and eicosanoid pattern. The anti-inflammatory pattern is associated with beneficial features of the immune system and accordingly with a remarkably shorter hospitalization than with the standard lipid emulsion. These results indicate that it is positive to establish fish oil supplementation protocols that provide maximum beneficial effects while adverse effects are minimized (Fürst & Kuhn, 2000).

Numerous reports substantiate the important role of amino acids and peptides. Tryptophan is probably one of the best examples for a classical nutraceutical. Except for its function as an essential amino acid tryptophan has been employed in many clinical and pathological situations as a drug. The occurrence of Eosinophilia-Myalgia-Syndrome (EMS) following tryptophan administration resulted in legal withdrawal from this amino acid. However, the real cause for the EMS symptoms is probably a dimer of tryptophan, 1,1′-ethylidene-*bis*-(tryptophan), a contaminant formed during the microbiological production of tryptophan (Belongia, Mayeno, & Osterholm, 1992).

Arginine, a non-essential amino acid received much current attention because of its potential immunostimulatory properties (Barbul, 1990). In certain clinical conditions arginine supplementation was associated with improved cellular immune response, increased rate of phagocytosis and maintenance of T-cell function. A daily pharmacological dose of arginine is claimed to be accompanied by retardation of tumor growth and less formation of metastases (Daly, Reynolds, Sigal, Shou, & Lieberman, 1990). Arginine is the direct precursor for nitric oxide (NO). NO is a relaxant of smooth muscle in vascular tissues and has been attributed to be responsible for inhibition of thrombocyte aggregation and adhesion (Reynolds, Thom, Zhang, Ziegler, Naji, & Daly, 1988). Inhibition of nitric oxide synthesis increased intestinal mucosal permeability in experimental models of ischaemia-reperfusion intestinal injury (Kubes, 1993) and acute narcotizing enterocolitis (Miller et al., 1993). In addition, administration of L-arginine reversed the effect of NO-synthase inhibition (Kubes, 1993). These results suggest that basal NO production is important in minimizing the mucosal barrier dysfunction in these models.

Arginine may also be of significance in the critically ill because of its potential role in immunomodulation (Evoy, Lieberman, Fahey, & Daly, 1998; Kirk & Barbul, 1990). It is hypothesized that arginine enhances the depressed immune response of individuals suffering from injury, surgical trauma, malnutrition or sepsis. In experimental animals, as well as in human studies, supplementation with arginine resulted in an improved cellular response, a decrease in trauma-induced reduction in the T-cell function and a higher phagocytosis rate (Kirk & Barbul, 1990).

Glutamine is the most prevalent free amino acid in the human body. Glutamine not only acts as a precursor for protein synthesis, but is also an important intermediate in large number of metabolic pathways. With the recognition that catabolic states are associated with intracellular glutamine depletion, various approaches to maximize glutamine nutrition were introduced. Since native glutamine is poorly soluble in water its administration is not practicable in routine clinical setting. Synthetic stable and highly soluble dipeptides show great potential as a way of providing glutamine which otherwise is difficult to deliver. Indeed, glutamine dipeptides are true nutraceuticals. Supplemental glutamine (dipeptides) exert many beneficial effects in clinical setting as summarized in Table 2 (for references c.f. (Fürst, 1998, 2000).

Future implications of glutamine (dipeptide) therapy are full of promise. A consistent observation is that glutamine-enriched parenteral feeding attenuates the expansion of extracellular and total body water. This interesting finding suggests that provision of glutamine

Table 2
The effects of glutamine dipeptide supplemented parenteral nutrition—clinical trials

	Observation
Nitrogen balance Weight gain in hematological patients Hepatic dysfunction during BMT Immunity	Improved
Protein synthesis	Increased
Expression of anti-inflammatory cytokines (IL 10) Lymphocyte proliferation	Enhanced
Muscular glutamine concentration	Maintained
Trauma related intestinal atrophy	Avoided
Chemotherapy induced mucositis Length of hospital stay Mortality Release of pro-inflammatory cytokines (IL6, IL8, TNF α)	Reduced

(dipeptides) may influence stress-induced accumulation of extracellular fluid by affecting membrane function and thereby changing the cellular hydration state—indeed, an encouraging future therapy in situations with extracellular edema (Häussinger, Roth, Lang, & Gerok, 1993; Schloerb & Amare, 1993). Experimental studies suggest that glutamine availability is an essential factor during conditions associated with glucose intolerance. During hyperinsulinemic euglycemia, increased glutamine availability blunted insulin action on glucose production and enhanced insulin-mediated glucose utilization (Ballard, Farag, Branum, Akwari, & Opara, 1996). Thus, glutamine (dipeptide) appears to possess a future potential to be of benefit as a nutrient adjuvant during clinical situations associated with insulin resistance, such as diabetes mellitus, sepsis, trauma and others.

A further fascinating approach proposes glutamine (dipeptides) as a suitable cardioprotective and rescue agent (Khogali, Harper, Lyall, & Rennie, 1998). The mechanism through which glutamine exerts its beneficial effects may involve maintenance of myocardial glutamate and thus glutathione as well as myocardial high energy phosphates and prevention of myocardial lactate accumulation (Khogali et al., 1998). The implication of these results might include the possible use of glutamine to support the heart during reperfusion initiated by thrombolysis or coronary angioplasty in patients with acute myocardial infarction. Furthermore, glutamine enrichment of cardioplegia during cardiac surgery might improve the postoperative ventricular function and the postoperative survival in patients with coronary artery disease.

3. Phytochemicals—nutraceuticals

The fascinating topic of phytochemicals is discussed in details in the present proceeding by Dr. Rechkemmer. Indeed, phytochemicals are also nutraceuticals per definition and in the present communication some interesting examplifications are indicated, how they provide medical and health benefits.

Glucose and insulin regulations are important features of phytochemicals and there are fascinating reappraisals of traditional treatment of diabetes. *Agrimonium eupatoia* extract exerts antihyperglycemic, insulin-releasing, insulin-like activity and stimulates incorporation of glucose into glycogen (Gray & Flatt, 1998).

New hypoglycemic compounds have been proposed like castanospermine, neomyrtillin (bilberry), myricetin (tea, berries, fruits). *Atriplex halimus* (saltbush) has been shown to benefit glycemic control (Day, 1998; Ong & Khoo, 1996). Actually, more than 1000 plants have been claimed to offer special benefits in the treatment of diabetes, few have received scientific investigations.

Since ancient time, mushrooms have been consumed by humans, not only as a part of the normal diet, but also as a delicacy because they have a highly desirable taste and aroma. In addition, the nutritional, tonic, and medicinal properties of mushrooms have been recognized for a long time. Certain ancient religious scriptures such as the Vedas have mentioned their medicinal importance. Romans considered mushrooms to be the Foods of the Gods and the Chinese declared them to be the "Elixir of Life" (Johl, Sodhi, Dhana, & Kapoor, 1995; Mattila, Suonpaa, & Piironen, 2000).

In recent literature medicinal values like antitumor, antiviral and hypolipidemic effects have been emphasized. The active antitumor agent is lentinan, a polysaccharide, characterized as β-1,3-glucan, having branching of the 1,6 bonds. The underlying mechanism is presumably an activation of the host's immune system. Lentinan also possesses antiviral activity due to an induction of interferon-γ production. Lentinan enhances host resistance against infections with bacteria as well as fungi, parasites, and viruses, including the agent of AIDS. Lentinan reduced the toxicity of AZT (a drug commonly used for treating HIV carriers and AIDS patients). Prevention of the onset of AIDS symptoms through potentiation of host defense is now being actively investigated both experimentally and clinically (Chihara, 1992; Kaneko & Chihara, 1992; Mattila et al., 2000).

It is obviously beneficial for wound healing to drop honey into the wound. Indeed, it may also exert protective effect on the acute alcohol induced gastric mucosal lesions when taken orally. The antimicrobial activity is due to flavonoids and phenolic acids (Sato & Miyata, 2000; Wahdan, 1998).

The role of traditional soy-food in disease prevention and treatment has gained worldwide recognition because of its antidiarheal, hypolipidemic, anticancerogenic and antiosteoporotic effects. Isoflavone phytoestrogens in soy, such as daidzein and genistein, are known to be responsible for the biological activities. High soy food consumption is associated with lower breast and prostate cancer risk and improves bone mineral content (Adlercreutz, 1995; Barnes, 1997; Karyadi & Lukito, 2000; Messina, 1999). Many of the observed effects are due to phytoestrogenic activities as certainly will be explained in detail by Dr. Rechkemmer.

Current studies from our laboratory demonstrate that the intestinal uptake of genistein is about 40%, whereas the uptake of genistin is lower corresponding to about 15% (Andlauer, Kolb, & Fürst, 2000a; Andlauer, Kolb, Stehle, & Fürst, 2000). The total uptake of isoflavones from Tofu, however only yields about 9%, probably due to the high content of malonyl-derivatives which are not taken up directly (Andlauer, Kolb, & Fürst, 2000b). A highly interesting novel finding is that the uptake of isoflavones can be considerably improved and the rate

of glucuronidation markedly reduced by adding phloridzin, a known SGLT1 inhibitor (Andlauer, Kolb, & Fürst, submitted for publication). Indeed, the concomitant isoflavone and phloridzin nutrition offers a promising novel method in designing functional food by using a combination of two or more nutraceuticals.

4. Conclusions

The current knowledge of the beneficial effects of nutraceuticals will undoubtedly have an impact on nutritional therapy. At present, nutraceutical represent the fastest growing segment of today's food industry. The market is estimated at 30 billion US $ growing at 5% per annum. The correct balance is struck between the exploitation of lucrative business (irresponsible market entrants) and adequate consumer protection (Hardy 2000).

Although it may be many years before the new designer foods will be stocked on supermarket shelves, the ongoing program will lead to a new generation of foods, which will certainly cause the interface between food and drug to become increasingly permeable. Thus, in the future we will see the emergency of nutraceutical soups, nutraceutical processed meat, bread and sausage. And many of these foods might be genetically produced. A horror vision for one—a fantastic fulfillment, indeed, for others.

The present accumulated knowledge about nutraceuticals represents undoubtedly a great challenge for nutritionists, physicians, food technologists and food chemists.

In the meantime there are obviously more questions than definitions: Which nutraceutical possess health preventing or health promoting properties and therapeutic potentials? Once identified, which limits are to be considered in order to avoid risks of health? Are combinations of nutraceuticals more effective than larger quantities of single nutraceuticals? Do additions of high amounts of natural beneficial compounds influence the taste and structure of nutraceuticals? May favorable properties of bioactive compounds-enriched nutraceuticals be maintained during routine technical processing?

Public health authorities consider prevention and treatment with nutraceuticals as a powerful instrument in maintaining health and to act against nutritionally induced acute and chronic diseases, thereby promoting optimal health, longevity and quality of life.

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