Functional foods. Reflexions of a scientist regarding a market in expansion♣

A. Monge. C IFA. Universidad de Navarra, 31008 Pamplona (Spain). cifa@unav.es., T. Cardozo (Bolivia), E.J. Barreiro (Brasil), P. Huenchuñir (Chile), R. Pinzón (Colombia), G. Mora (Costa Rica), A. Núñez (Cuba), X. Chiriboga (Ecuador), A. Cáceres (Guatemala), G. Rivera, V. Bocanegra-García (México) UAM-Reynosa-Aztlán, Universidad Autónoma de Tamaulipas, 88740 Reynosa (México), M. Gupta (Panamá), E.A. Ferro, I. Peralta (Facultad de Ciencias Químicas, Universidad Nacional de Asunción Paraguay), O. Lock, D. Flores (Perú), L. Salazar, O.D. Guzmán (Salvador), H. Cerecetto, M. González (Uruguay).

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RESU M EN. The International Union of Pure and Applied Chemistry (IUPAC) decidió en 2006 impulsar el estudio en América Latina de los nutracéuticos como una oportunidad científica y de interés comercial para toda la comunidad. La inciativa, impulsada por el *Subcommittee on Medicinal Chemistry and Drug Development* de la IUPAC, presidido por C.R. Ganellin, ha permitido unir esfuerzos de investigadores de América Latina. El proyecto se ha realizado con una presentación general del tema, que se corresponde con este trabajo, al que seguirá inmediatamente una publicación acerca de la situación concreta en diferentes países de la región. El trabajo se presenta de forma simultánea en distintas revistas de manera que se facilite el acceso a él y su siguiente discusión por parte de los interesados, en un intento de crear un clima de interés por el tema sobre la base de la investigación de conocimientos tradicionales y experiencias científicas que permitan la innovación en beneficio de todos, muy especialmente, de las sociedades productoras, así como de las personas que precisen de los compuestos.

ABSTRAC T. In 2006, the International Union of Pure and Applied Chemistry (IUPAC) decided to promote the study of Nutraceuticals in Latin A merica as a scientific opportunity of commercial interest for the entire community. This initiative, promoted by the IUPAC Subcommittee on Medicinal Chemistry and Drug Development, chaired by C.R. Ganellin, resulted in Latin American researchers uniting efforts to successfully carry out this study. This project consists of a general presentation of the topic of this study which will be followed by the publication of specific situations in different Latin A merican countries. The work is easily accessible as it is presented simultaneously in different scientific journals. This permits readers throughout the world to enter into discussion regarding the topic published, creating a climate of interest based on research of traditional knowledge and scientific experience which permit innovation to the benefit of all, especially the nutraceutical producer societies and those who are in need of the compounds.

DEFINITIONS

The term, nutraceutical, is the result of a contraction betw een nutrition and pharmaceutical. In 1989, Dr. Stephen D efelice defined nutraceutical[1] as ''any substance that is a food or a part of a food and provides medical or health benefits, including the prevention and treatment of disease''.

Not long after, the definition was modified by Health Canada, defining nutraceutical as ''a product isolated or purified from foods, and generally sold in medicinal forms not usually associated with food, and demonstrated to have a physiological benefit or provide protection against chronic disease''.[2] In the Merriam-Webster Dictionary this term is defined as ''foodstuff (as a fortified food or dietary supplement) that provides health benefits in addition to its basic nutritional value''.

Functional Food (FF) will be that which has a beneficial effect for health, be it for its constitution or for having added a nutraceutical to the original foodstuff, more specifically in certain societies of the Latin American continent. Thus according to Health Canada[2] a FF is ''consumed as part of a usual diet that is similar in appearance to, or may be, a conventional food, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functionsõ (beyond energy and essential nutrients). For example, yogurt w hich promotes beneficial microflora in the gut; cereals that provide a significant source of

♣This paper is published in attention to request of Dr. Alberto Núñez Sellés, President of Cuban Society of Chemistry, to correspond to IUPAC call to promote the study of nutraceuticals in Latin America.

fibe believed to decrease the risk of certain types of cancer;papaya, which contains papain, and helps the digestion of protein and provides other benefits (see below).

BACKGROUND

The concept of FF is very old (''Let food be your medicine and medicine be your food. Whosoever gives these things no consideration and is ignorant of them, how can he understand the diseases of man''. Hippocrates ca 400 B.C.),[3] and the interest in these compounds appears in Japan in the mid-1980s, w ith three objectives:

1) Control of health costs.
2) Improvement of quality of life.
3) Life expectancy.

Indeed, the term functional food w as first introduced in Japan and refers to processed foods containing ingredients that aid specific bodily functions in addition to being nutritious (Foods for Specified Health Use, FO SHU).[4]

This interest is reflected in the transition from the ''Baby Boomers'' of the 60's to the ''Older Boomers'' of the 21st century in which there is an awareness of a longer life expectancy, and consequently, a proposal is made, not so much as to search for a cure for diseases but rather to provide health-enhancement and to live under the best possible circumstances.

D EVELOPED SOCIETIES ''VERSUS'' DEVELOPING SOCIETIES

In the past few years, intake of FF has increased considerably and it is a grow ing market. The attitude of developed societies manifests itself in the preoccupation that they have for the intake of these types of food, which have beneficial properties, or other foodstuff which incorporate extracts or compounds such as vitamins of interest.

In addition, they are preoccupied w ith avoiding the ingestion of saturated fats, controlling alcohol intake, doing daily exercise, etc., all of which forms that which is sociologically defined as a type of emerging society in this 21st century. The pathology of this type of behavior is reflected in the condition identified in 1997 by Dr. Steven Bratman called Orthorexia, which is defined as a recently discovered mental illness, related to ''healthy eating habits'' or an obsession for ''healthy foods''.[5] The prototype involves a person from a developed country, w ith a good level of education, who is quite demanding in character, and preoccupied with showing a good physical image before third parties.

The situation is quite different in the developing countries in which the intake of FF is related to nutritional problems and hunger, as well as a lack of medicinal agents due to difficulties of economic means. There are millions of people for which these compounds not only prevent a loss of health but are, in fact, the only form of treating a disease.

Many of these foods that are under consideration can be treated with phytochemicals, extracts that are added to food such as in the case of fruit juices. With regards to variety as w ell as quantity, the majority of these plants are located in the developing countries.

We are living in an important situation in which the developed countries are very interested in goods that can be made available from the developing countries. It might be opportune to appeal to corporate social responsibility so that both the developing and developed countries recognize the possibility that exists for mutual benefit.

For this type of action, it is important to acknow ledge that food is considered a universal good, and that the fight against hunger is considered a priority action, according to the Declaration of the Millennium of the United Nations.[6] Of no less importance is the fact that the shortage of food and drugs results in social instability. The FF not only offer the possibility of obtaining economic benefits regarding goods in w hich w e all have great interest but they also aid in the attempt to solve the problems of health and hunger by means of adequate management of these types of foods, in which many people from different countries and situations are involved

CONSIDERATIONS REGARDING QUESTIONS TO BE SOLVED

The origin of these phytochemicals implies that the know ledge regarding their use has been in the hands of native communities during many years and w ho only lack the definition of specific criteria recognized by the developed societies in order to attain universal use of these FF.

There are three principal questions to solve. First of all, there is the question of scientific validation and verification of the claims that inform the consumer of the product activity under consideration. The second question involves the need to determine if the activity being claimed can be obtained at the doses ingested w ith routine intake of the food. The third question to be solved is related to the safety issues;nothing justifies the affirmation that a natural product is equivalent to a non-toxic product.

It is also important to remark that the questions related to justice should be considered.

It is necessary to offer the means by which the entirew orld can have access to the FF regardless of the differing economic development of countries. It will also be necessary to assure that these FF reach everyone, be they men, women, children or the elderly, a task that is not always possible in all societies. These are questions related to Distributive Justice.

Other approaches related to social justice can also be raised. One such example is the case of participating in decisions regarding development, which implies caring for matters related to biodiversity and assuring that there is a fair distribution of benefits, something that is not always easy to do due to historical differences in the development of societies.

Some questions that are necessary to take into consideration for the developing countries are related to the possibility of consuming goods which they have known and used for a long time and which, upon industrialization, could end up outside their possibilities for acquisition. Another important situation to consider is that 90 % of the plants, which are cultivated in developing countries and can be used as FF, would be subject to uncontrolled consumption, which is not sustainable; this implies serious problems leading to shortages of the plants during the industrialization processes. No less important is the question regarding the possibility of adulteration during the process of industrialization due to an increase in demand, drought, ...etc. which may lead to the substitution of the target species for other closely related ones.

With regards to this matter, it is important to quote the excessive number of intermediate handlers ('middlemen') which occurs in the industrialization and commercialization of the FF as it greatly prejudices both the

native communities at the beginning of the production chain and the consumers at the end of the chain.

OPPORTUNITY FOR SCIENTIFIC INVOLVEMENT IN FF, IN RELATION TO THE DEVELOPING COUNTRIES

There is great social demand for a commodity that is considered to be of interest for people's health. Today's society is aware of the need to act w ith distributive justice guidelines. The past recalls other actions in w hich the exploitation of some people by others reigned. The media, sense of freedom, human rights, ...are obliged to act, follow ing new social criteria. The ethical considerations in business activity are not just simple decoration, but rather a guarantee for all companies.

Socially, the FF are a reality perceived by society throughout the entire world and they can be clearly defined as a meeting place. Technically, today it is possible to respond to the demands of safety and efficacy for which society clamours.

GENETICALLY MODIFIED FUNCTIONAL FOODS

The economic and social importance of FF has favoured a new approach to the genetically modified foods so as to improve the production of the compounds w ith biological activity that are of interest for health.

The World Food Summit in Rome in June 10-13, 2002 affirms that ''we are resolved to study, share and facilitate responsible use of the biotechnology with the decision to meet the necessities of development''.

C urrent examples are both numerous and important. A classical example is know n as ''golden rice'', a variety of rice that accumulates carotenoids w ith pro-vitamin A activity. The objective is to introduce it in Asia in order to solve problems of vision as well as learning difficulties in children. This approach is based on the design of gene transfer vectors, especially designed for a given aim, but that in addition, implies jumping the barriers that separate the species, with their possible consequences. Consider, for example, the expression of genes in a vegetable in which said genes originate from the genome of an animal and are consumed by vegetarians; or the expression of genes originating from pig genome and are consumed by Muslims, ...

With regards to the developing countries, it will be necessary to consider if the abandonment of cultivating indigenous varieties, due to substitution of other genetically modified varieties, would imply a dependence on manufacturers and the loss of natural biodiversity.

THE FF IN THE LATIN AMERICAN REALITY OF THE 21st CENTURY

The Latin American region extends from Mexico to Chile and Argentina. It includes a good number of countries of diverse geography but they possess a long history, with native settlements of important cultures, which have left transcendental testimonies of their development. The biodiversity and enrichment of flora and fauna is an easily contrastable reality.

It is easily understood that these tw o realities have resulted in an important culture in the application of plants, in health-related treatments, with innumerable oral and written testimonies to the curative effects of plants. Quinine, for the treatment of malaria, is probably the example of reference.

Traditionally, plants have been associated with medicinal agents and hence the interest shown by Medicinal Chemistry. The idea was to isolate and optimize compounds synthesized by plants for clinical use.

The approach that was proposed was very difficult to carry out. It involved considering individualized compounds which would be included in human clinical usage, after meeting all the requirements needed in order for them to be licensed for marketing. The challenge is not an easy one. One must keep in mind the fact that the product which is finally introduced into clinical trials is usually a chemical modification of that w hich was originally found in the plant. Consequently, there is a loss of interest in the original material of vegetable origin.

The scenery is very different when considering FF. In this case, work can be carried out on the plant itself in such a way that the final product can develop completely within the developing countries; this results in local grow th and maintains the biodiversity.

The Latin American wealth in plants w ith potential application as FF is remarkable, for its variety as well as for the associated traditional know ledge regarding the plants.

This w ork presents a selection of examples which, although somewhat limited, is certainly representative of countries. The objective of this contribution is to encourage companies and researchers to consider the importance of the issue and to take an interest in it.

The situation is problematic because in many cases the information regarding the use of the plants by the shamans is not available because this knowledge corresponds to the cultural heritage of these native groups and they are apprehensive when it comes to revealing discoveries that belong to their cultural heritage. This situation is especially important and representative of the Amazon, where there are isolated groups that have their own languages, social structures, and nutritional habits. It is interesting to see how different isolated tribes use the same plants for the same use. For example, in the treatment for obesity,[7] the Yanumansi from the Venezuelan part of the A mazon (250 persons) use *Smilax dominguensis* in the same way as the Aba Conoeiros of Brazil (Fuentes del Totacntis)(50 persons)or as the Mamainde, also Brazilians (Rondônia-Alto Rio Curimbiara) (200 persons). Another example could be the use of *Turnera ulmifolia* for the treatment of something as generic as debility by the Apiaca of Brazil (Mato Grosso Norte (100 persons)or by the Kayapu (200 persons), also from Brazil (Moto Grasso) or by the Maku (300 persons) from the valleys of U neiuxi del U rubaxi in Brazil, or by the Piriutiti (110 persons) of Rio Curian or by the Sinabo (320 persons) of Bolivia (Bajo Yata). Far from the Amazon, in Mexico, (Chihuahua) the Tarahumaras (500persons)also use this plant for the same purpose.

One has to ask how much of the above information can truly be used to benefit the groups of people who are using the plants for such purposes. In addition, we must become convinced of the need to add experimentation to the observations of traditional medicine so that scientific evidence related to the efficacy and lack of toxicity of these plants in their use as FF and/or nutraceuticals can be found.

With regards to these countries that are so rich in biodiversity, it is important that the aforementioned comments regarding experiences based on human

groups composed of small numbers of people be verified by official science. C ontinuing on with the area of the Amazon and focusing on Brazil, one example to be considered is *Taraxacum officinale*, an *Asteracea* containing a family of compounds which are claimed to be an antioxidant, have antiinflammatory and diurectic effects, and even be useful in the treatment of diabetes, without having scientific evidence to back up these claims,[8] and yet with well-known side effects and interactions.

This plant, known as Dandelion (Diente de León), is abundant throughout the Northern hemisphere and is cultivated in East European countries such as Bulgaria, H ungary, Poland, Rumania. It is used in the form of infusions, decoctions of the roots and also extracts from the leaves. This is an example of a plant that presents activity of interest that is still not confirmed and w hose side effects should be taken into consideration, and yet it is being used with clear benefits of exploitation. It is an example of a relationship between different societies and continents that clearly reflects the difficulty regarding the establishment of the therapeutic use and innocuity of a plant regardless of the society being considered.

In Bolivia, a tuberose crop, known as ''Racacha'' or *Arracacia xanthorriza*, is aplant which is used in Brazil in the production of starch, used in the manufacturing of pap for babies. It is a typical example of how a community, in this case the local people of San Juan de la Miel, with Bolivian institutional support, has attained conservation of the plant and promoted new forms of consumption. Racacha is rich in minerals and vitamins A and B, in calcium and phosphorus. It is easily digested and is indicated for convalescents and the elderly. Racacha roots are used as the basis of a food regime in the district of Coroico, accompanied by yacón (*Smallanthus sonchifolius*) juice; yacon is a sweet root vegetable whose pulp contains inulin, an agent that can be related to the control of diabetes.[8,9]

The claims made regarding the nutritional value of Racacha are that it is an ''energy dessert that boosts the immune system and prevents infections''. It is necessary to demonstrate w hether or not these claimed benefits correspond to the traditional use of the plant.

The institutional support given to the cultivation of Racacha has helped to improve the species and their industrialization[10] benefits the Andean countries. This is a clear example of how technical aid offers the opportunity for the development of societies.

Sarsaparilla, *Kajahuatena* (Smilax regeli Killipel Morton Griseb), is another example of a root frequently used in America for its diuretic and purifying effects and is also known to be effective in the treatment of psoriasis. Both the root and the rhizomes are used. It is not surprising to see the great efforts made by governments, such as that of Bolivia, for the development of studies related to the production and determination of the properties of these plants w hich have been known in their society for a long time.

The American continent is very rich in fruits that can be used in food regimes, in their original form as well as in the form of juices. One example is Papaya (*Caraica papaya*), of Mexican or Andean origin, according to diverse authors. Its use has extended throughout the entire w orld. Papaya pertains to C aricaceas and consists of 70 species. It is known for its content of papain which helps the digestion of protein, and it is also a source of potassium, vitamin C , pro-vitamin A and fiber.

While papaya is w ell extended throughout the w orld, knowledge regarding Noni juice (*Morinda citrifolia* L.) is different;the latter has been recognized for over 2 000 years in many villages, cultivated throughout Central America, and commercialized by different companies.[11] According to traditional knowledge, it has beneficial effects, believed to be useful in treating hypoglycemia, cholesterol levels, menstrual cramps, blood pressure, etc.[12] It is also a typical situation that demonstrates the resistance of developing societies to further study on traditional activities. Nevertheless, Noni juice is commercialized throughout the entire world, but at an elevated price. It is an example of a plant that not only has possible beneficial effects for health but is also commercial. The climatic conditions of the Caribbean are very favorable for this crop. This plant is an example of a value-added crop whose complete process from cultivation to market can be carried out in developing countries, thereby contributing to their industrialization.

Guayaba (Psidium spp.), guava in English, is one among more than 100 very popular species in Central America and the Caribbean. The trees of the Myrtaceae family produce an edible fruit that contains vitamins A, B and C ;Psidium guajara is the most popular.[13]

It is often used as an anti-influenza agent. This fruit is used in an ample variety of foods, frequently found in yogurt dairy products. In Mexina Calvillo, Aguascalientes, México, within the Huajacar valley, the most important plantations of Guayaba are found. This could be considered a model of high yield sustained agriculture where, in addition to the beneficial effects of the fruit as an FF, the possibility of attaining great benefits for the development of the country can be taken into account.

Mango (*Mangifera indica* L.) is also an important fruit but, at present, the application of mango bark is considered for a pharmaceutical preparation (Vimang), made in Cuba.[14] This preparation is a raw extract with antioxidant, analgesic, antiinflammatory and immunomodulating activity. The activity has been demonstrated in more than 7 000 patients during a period of ten years (1994-2004). It is a clear example of the use of natural resources because, in addition to the fruit itself which has its interest in nutrition, the Cuban scientists have extended their studies and carried out scientific experimentation based on traditional observations; this offers the opportunity to introduce new products, as nutraceuticals or FF, in health treatment.

Naturally, w hen considering medicinal application of a plant, it is necessary to gather information that comes forth from its traditional use. One such case occurs in Costa Rica de Hombre Grande (*Quassia amara* L.ex. Blom). This plant, which extends from Mexico to the Amazon, is used in Europe as an appetizer, diuretic, and agent against dyspepsia and anorexia among others, which allow s it to be considered as a nutraceutical.

It also has an important use as an insecticide,[15] as can be deduced from the important importation of this plant for such use by the USA since 1940. The latter example offers a good reason to develop and preserve the biodiversity of these countries in addition to promoting research for additional uses other than the traditionally observed medical use.

INDUSTRIALIZATION OF FF

Industrialization of FF is an important question that should be considered w ith great care, for the benefit of the developing countries. For example, in Mexico, the

plants w hich are traditionally used for medicinal purposes are estimated to number 3 000 (approximately 10 % of the country's plants), of which the number estimated to be commercialized is approximately 250;[16] principally, their origin is in the central and southern areas of the country.

The project, ''Mercados Verdes Herbolarios'', supported by the USA is an example where farm workers have acquired the ability for the sustained use and management and in the processing of medicinal plants. However, as Bentacourt cites,[17] studies on this material that also consider the commercialization of these plants are scarce.

It is important to appreciate that if the use of plants for health purposes does not include industrial exploitation it will be impossible for them to reach societies which need them, and there will be no profitability for the societies that possess the plants. Likewise, a series of actions common among all countries is required for the management of plants as nutraceuticals or FF. In general, there is a need for national programs such as PRONAPLAMED (National Program of Medicinal Plants), in Mexico. The objective of these types of programs is to guarantee sustained cultivation, which permits conservation of the plants and an improvement of the species, whenever possible. It should be kept in mind that a great number of these plants that are used for nutraceuticals or FF are wild plants. In addition, the growers should be educated in this matter because, if not, certain aspects will be negatively affected. One such example is the quality, which is sometimes affected, during the process ''plant to finished product''. This is largely due to lack of knowledge or poor habits which are sometimes observed in the handling of the plants.

One possible solution for these cases lies in the formation of microcompanies, an activity much used today in developing countries; they are becoming accepted by the cultivators as they are beginning to realize the need for them. There is a need for technology for the different phases that are involved in the preparation of these compounds. Important questions such as storage and treatment can be real problems when there is a lack of properly ventilated warehouses, refrigerators, ... etc.

The reasons behind the interest show n in plants by the national companies appear to be commonly shared by the native population w hereas the transnational companies only seem to show interest in relation to the sectors that possess adequate economic availability.

In the Latin American countries a series of common characteristics appears, one being that their great tradition in the use of plants as FF or nutraceuticals corresponds to only 10 % of their rich variety of plants. The most immediate consequence in this world of climatic changes and general aggressions on nature is the danger of losing the species.

The countries being considered here have formed organizations that support the producers, which principally refers to the training of the cultivators, the sustained management of the plants and proper production of the final product. It should always be kept in mind that this action for the development of communities will result in good products, and efforts should be made so that the products may have the greatest possible added value. Producing fruit is not the same as producing juice, and the trade of plant extracts reduces the transportation costs and increases economic profit when compared with the commercialization of plain dried vegetable materials. Such development, in many cases, is out of the reach of plant producers and requires a technological input in order to establish, optimize and scale - up such processes. Organizations are being established through the creation of microcompanies in all of these countries and they reflect a great sense of solidarity.

The training of these cultivators is becoming an important aspect of this action because in many cases, the plants are wild and there is a possibility of unscrupulous exploitation which, in some cases, could result in mixing up some plants with others in a fraudulent attempt to satisfy possible market demands. An additional risk associated to this issue is the permanent lost of valuable species in their natural environments, which is a patent problem when roots are the organs of traditional use. The increasing concern in environmental affairs of the population from developed societies –consumers of natural resources produced in developing countries– could effectively contribute to the preservation of such resources, demanding the sustainable production of the raw material for the production of nutraceuticals and phytomedicines.

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