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Introduction

The Increasing Demand for Functional Foods

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1.1 Food Patterns: A Cross-sectional Approach and Brief Overview

Primitive societies often lack resources but have always emphasized the role of nutrition in maintaining good health and wellbeing (Balch 2006; Murray & Pizzorno 2005, 2012). So, the idea of a balanced and wholefood-enriched diet to ensure homeostasis and improve life expectancy is not new.

Concomitantly with the intensification of the globalization process and advances in the food industry, a pronounced increase in public health problems has been observed. Health-related economic and social costs have risen to represent a significant percentage of worldwide expenditure (American Dietetic Association 2009; Arvanitoyannis & Houwelingen-Koukaliaroglou 2005). Public health problems affect all sectors of society – elderly, adults, children, and adolescents. Therefore, the deployment of prevention strategies seems to be essential, not only to avoid the progression of this worldwide problem but also to try and restore the balanced food patterns and proper lifestyle of individuals.

Infectious diseases were the most frequent causes of morbidity and mortality among the first civilizations, mainly attributed to poor hygiene conditions, and efforts were made to reduce the incidence of outbreaks of infection and epidemics. Nowadays, research is carried out to find even more effective and specific chemical drugs, allegedly able to treat modern disorders, although most of them can be eradicated just through lifestyle modifications. Metabolic disorders and related problems are some of the most important current contributors to human morbidity and mortality. Overweight and obesity, considered the epidemic of the 21st century, increasingly affects all age groups, with children being the most vulnerable (Arvanitoyannis & Houwelingen-Koukaliaroglou 2005; Bagchi 2006).

Hippocrates said that “whatever be the father of a disease, the mother is always a bad diet” (Longe 2005; Murray & Pizzorno 2005, 2012). Linked with the increasing incidence of metabolic disorders has been a demand for new food products. Addictive behavior,
feelings of pleasure, and palatability are the main determinants of food choices in modern civilization (Balch 2006; Jauho & Niva 2013; Murray & Pizzorno 2005). Thus, it is not surprising that rates of chronic disorders, most of them food pattern related, have reached epidemic levels, and are likely to increase in the coming years.

1.2 Nutrition and Health: Facts and Tendencies

1.2.1 Evidence-based Medicine: Past to Present

There are numerous reports and historical manuscripts proving data about the applications of botanicals and plant food preparations, for both nutritional and medicinal uses (Khan & Abourashed 2010; Longe 2005; Murray & Pizzorno 2012; Vanaclocha & Cañigueral 2003). Traditional medicine dates back to the dawn of human civilization; primitive societies used botanical preparations and even plant food derivatives for medicinal, culinary, preservative, and aromatizing purposes (Ferreira et al. 2009; Junio et al. 2011; Rubió et al. 2013; Sahib et al. 2013; Spelman et al. 2006; Sung et al. 2011; Viuda-Martos et al. 2010; Zheng & Wang 2001). Numerous attributes were conferred on ethnopharmacological preparations, which have been increasingly validated through epidemiological, preclinical, and even clinical studies (American Dietetic Association 2009; Ferguson 2009; Sung et al. 2011; Viuda-Martos et al. 2010). Primitive societies gained knowledge about identification, culture and ideal harvesting conditions, indications, contraindications, side-effects, and toxicity of natural products, as well as recommended dosages (Balch & Stengler 2004; Balch et al. 2008; Murray & Pizzorno 2012; Vanaclocha & Cañigueral 2003). Therefore, early civilizations discovered a multitude of natural product potentialities and applications but because of the lack of scientific evidence, they could not pinpoint the main responsible active principles. More recent researchers, aiming to deepen knowledge in this area, have often used previous findings to guide their current studies.

In relation to the nutritional and medicinal use of natural products, it is important to highlight direct consumption as part of the daily diet but they are also used as flavorings, preservatives, flavor intensifiers, and so on (Balch 2006; Balch & Stengler 2004; Khan & Abourashed 2010; Longe 2005; Murray 2004; Murray & Pizzorno 2005; Vanaclocha & Cañigueral 2003). Research has been focused not only on their health improvement effects but also their organoleptic properties.

In spite of cultural, ethnic, and religious patterns, the importance of a balanced diet is clearly evident. Since earliest times, human beings have understood that a balanced diet is crucial to survival and to maintain good health and wellbeing (Balch 2006; Murray & Pizzorno 2005, 2012). Dietary information has been passed through generations. The difference between edible and nonedible products was determined over time, including toxic potential and unpleasant side-effects. Different forms of preparation and cooking were developed, including the use of botanicals as herbs and spices to improve taste and general acceptability of food. At the same time, ways to improve the shelf-life of numerous products were found, and to prevent the occurrence of organoleptic changes (Balch & Stengler 2004; Khan & Abourashed 2010; Murray 2004; Murray & Pizzorno 2005). The discovery of the prophylactic and therapeutic potentialities of botanicals required thousands of years of observation and analysis. There are no doubts about the direct
impact of a balanced diet and lifestyle to ensure good health and wellbeing. In fact, 2500 years ago, Hippocrates highlighted the real value of nutrition, of health-conscious eating habits, and adequate preparation of meals as important contributors to long-lasting wellbeing (American Dietetic Association 2009; Biziulevičius & Kazlauskaitė 2007; Sung et al. 2011; Wegener 2014).

Over the years, the number of studies into botanical functionality, natural products, and their bioactive potential has increased in an exponential manner (Balch 2006; Balch & Stengler 2004; Balch et al. 2008). Different civilizations possess characteristic health doctrines and therefore different ways to prepare meals, mainly derived from perceptions about the intellectual, physical, energetic, therapeutic, and culinary applications of food (Kaput 2008; Murray 2004; Murray & Pizzorno 2005, 2012). With the globalization process, many local food habits have been changed and intercultural relationships established (Murray & Pizzorno 2005, 2012). Not all of this was bad but in relation to health and nutrition, a positive correlation between modified food patterns and prevalence of diseases and organic disorders has been increasingly stated over recent years (Arvanitoyannis & Houwelingen-Koukaliaroglou 2005; Fenech et al. 2011; Jones & Varady 2008). Neurodegenerative, cardiovascular, metabolic and immune diseases, and aging-related conditions, represent the most frequent and serious disorders, at a public health level (Ergin et al. 2013; Murray & Pizzorno 2012; Nasri et al. 2014).

It is important to bear in mind that geographical, cultural, and ethnic differences produce pronounced variations at genetic, molecular, and organic levels (Balch et al. 2008; Longe 2005; Murray & Pizzorno 2005, 2012). People living in distinct areas have specific genetic patterns and therefore different metabolic pathways and related responses to ingested foods (Fenech et al. 2011; Ferguson 2009; Kaput 2008). There are increasing evidences related to the effects of the interaction between foods and the individual's genome (nutrigenomics), leading to consequences at the level of the phenotype. This explains why a particular dietary practice may be appropriate for one individual and inappropriate for another (Fenech et al. 2011; Kaput 2008). On the other hand, the effects of genetic variations on dietary responses (nutrigenetics) have also been increasingly reported (Fenech et al. 2011). Based on these factors, increasingly detailed studies have been developed to improve the correct usage of plant food products, to discover their main active principles and mechanisms of action, and to widen perspectives about their use not only for prophylactic but also therapeutic purposes. Although genetics have some influence, environmental and lifestyle patterns are the main triggering factors which disturb organic homeostasis and thus affect the occurrence of disorders and diseases.

1.2.2 Modern Food Patterns: An (Un)Healthy Yield

Bearing in mind the previous explanations, and considering the increasing worldwide health-related economic and social costs, relating to medical devices, drug discovery, and other pharmacological advances (American Dietetic Association 2009; Arvanitoyannis & Houwelingen-Koukaliaroglou 2005; Bagchi 2006; Bigiardi & Galati 2013), research and industrial modifications have been increasingly implemented in attempts to control this serious problem. With the increasing rates of chronic disorders, more specific and more effective drugs needed to be synthesized, tested, and evaluated, to assess their possible application in humans (Holst & Williamson 2008; Khan et al. 2013;
Experimental drug studies need to be conducted for proper evaluation of their side-effects and related toxicity. However, much more important than medical and/or chemical drug interventions is the effect of dietary patterns and lifestyle (Balch 2006; García-Elorriaga & Rey-Pineda 2013; Kaput 2008; Sung et al. 2011).

Currently, several foods have been shown to be potent contributors to improving the health status and wellbeing of consumers and, at the same time, are able to reduce the incidence of social, and economic costs of noncommunicable and disabling disorders (Das et al. 2010).

The use of foods with known beneficial effects is important to improve the shelf-life and safety of numerous foodstuffs, and consequent reduction of the likelihood of side-effects, and also their organoleptic properties (Bagchi 2006; Bigliardi & Galati 2013; Jones & Varady 2008). Furthermore, in some instances, those products/substances can modify the acceptability of other products, making them more attractive. Herbs and spices (Barros et al. 2011; Morales et al. 2013; Rubió et al. 2013; Viuda-Martos et al. 2010), mushrooms (Ferreira et al. 2009; Heleno et al. 2015; Ribeiro et al. 2015), and oilseed fruits (Contini et al. 2012; Preedy et al. 2011; Siqueira et al. 2012) have been extensively studied and used not only to improve the nutritional value and shelf-life of many other products but also for their organoleptic properties, among many other benefits, some of which are still being investigated. It is interesting to highlight that, being themselves already considered functional foods, they also contribute to the health benefits, applications, and claims of many other food products (Arvanitoyannis & Houwelingen-Koukaliaroglou 2005; Bigliardi & Galati 2013; Siró et al. 2008).

Thus, functional foods are important in the daily consumption of a balanced diet, and also for their inclusion in many other edible products. The verification of the bioactive potential and other qualities of modified food products, and general consumer acceptability, are among the most promising fields in biotechnological and food industrial research.

1.3 Functional Foods Diversity and Related Applications: A World of (Un)Explored Biofunctionalities

Over the years, the study of the bioactive properties of edible matrices has increased exponentially, in association with scientific evidence that confirms their wide variety of applications and benefits that were promoted by folk medicine and primitive societies but lacked solid foundation and scientific validation (Balch 2006; Murray 2004; Murray & Pizzorno 2005).

Nutritional composition, in terms of proteins, lipids, carbohydrates, dietary fibers, vitamins, minerals, and other micronutrients, and also secondary metabolites, mostly existing in vestigial amounts, has received special attention (Mishra & Tiwari 2011; Murray & Pizzorno 2005; Rubió et al. 2013). Observational, longitudinal, and cohort studies have been conducted, in which not only nutritional but also therapeutic properties were observed (Balch 2006; Murray & Pizzorno 2005). The positive effects of the Mediterranean diet on cardiovascular health have been determined, through preferential consumption of wholegrains, seeds and nuts, fruits and vegetables, and cold-pressed oils (Murray & Pizzorno 2005; Yildiz 2010). These foods are extremely rich in beneficial nutrients, such as soluble and insoluble dietary fibers (promote healthy bowel function,
improve glycemic and blood cholesterol index, etc.), mono- and polyunsaturated fatty acids (act as neurocognitive, cardiovascular, endocrine health improvers, etc.), vitamins and minerals (essential nutrients which promote enzymatic and metabolic function, etc.) (Balch 2006; Murray & Pizzorno 2005). However, there are many other chemical constituents that can improve these functions and provide other bioactive properties.

Antioxidant, antimicrobial, antitumor, antiseptic, antiinfectious, antiinflammatory, hepatoprotective, antiadipic, and neuroprotective effects are among the most commonly assessed bioactive properties of the minor constituents of natural matrices. Intense investigation still continues in this field; numerous bioactive constituents have already been identified, including their mechanisms of action and biochemical interactions, but there are thousands of secondary metabolites that still remain unknown, and therefore need to be explored (Arif et al. 2009; Choudhary & Atta-ur-Rahmant 1999; Coman et al. 2012; Mishra & Tiwari 2011; Murray & Pizzorno 2005). The increasing demand to assess the beneficial effects of foods and their bioactive molecules is largely driven by increasing evidence of side-effects and adverse reactions produced by pharmaceutical drugs (Balch et al. 2008; Coman et al. 2012; García-Elorriaga & Rey-Pineda 2013; Palombo 2011; Sangamwar et al. 2008). In fact, many synthetic molecules were previously isolated from natural sources and then synthesized for large-scale production.

In the last decade, different terms have been adopted for natural products with specific and recognized functions in the human body. Although no general consensus has yet been established, the terms “functional food” and “nutraceuticals” have become a focus of attention for the scientific community and consumers (Bagchi 2006; Murray & Pizzorno 2005; Nasri et al. 2014). A functional food is commonly thought of as a food included in the normal diet which has one or more target functions in the human body, being able to improve the health status and/or reduce the likelihood of disorders occurring (Bagchi 2006). Such food should provide those benefits in the amount that can be expected to be ingested in the daily diet; therefore, they cannot be pills, capsules, syrups, etc. but should be part of a healthy food pattern (Bagchi 2006). A functional food can also be a natural/whole/unmodified food or food component in which a specific constituent has been added and/or removed by biotechnological or technological processes (Bagchi 2006; Nasri et al. 2014). Furthermore, it can also undergo various manipulations in order to modify or alter the bioavailability of specific constituents, focused on the improvement of its health benefits (Bagchi 2006; Bigliardi & Galati 2013; Das et al. 2010).

Overall, despite all these advances, the field of functional foods research still remains a real challenge. However, to improve the accuracy and applicability of current findings, health professionals, nutritionists, food industries, and regulatory toxicologists should work together, aiming for the goals of health promotion and disease prevention.

1.3.1 Food and Dietary Supplements, Botanicals, and Nutraceuticals: Clarifying Misinterpreted Concepts

The beneficial effects of diet-specific components and related scientific studies that support these findings lead to increasing interest in developing more specific tools and related technologies to improve and maintain an optimum level of health and wellbeing. However, several misinterpretations still exist. One is related to the correct definition of food supplements, botanicals and related preparations, and nutraceuticals.
The term “nutraceutical” is a combination of the terms “nutrition” and “pharmaceutical,” and refers to food/botanical ingredients or extracts that have defined physiological effects (Bagchi 2006; Nasri et al. 2014). So, in general, nutraceuticals are substances which provide beneficial effects not when consumed as part of a normal diet (functional food), but when consumed in unitary pharmaceutical doses, such as tablets, capsules, syrups, and so on (Bagchi 2006; Espín et al. 2007).

On the other hand, the term “food supplement” refers to concentrated sources of nutrients and other specific substances that have nutritional and/or physiological effects, in which the main goal is to supplement/enrich the normal diet. Food supplements may be beneficial to correct nutritional deficiencies, to maintain an adequate intake of certain nutrients or even to ensure a healthy status. But it is also important to be aware that in some cases, excessive intake of vitamins, minerals, and other vestigial micronutrients may be harmful, inducing undesired side-effects and even toxicity. Following the current nutritional guidelines is of the utmost importance in order to ensure their correct and safe use in food supplements (EFSA 2015a).

Lastly, many health claims have been put forward for botanicals and plant-derived preparations, typically labeled as natural foods, most of which arise from their ancient use by primitive societies. In line with the scientific evidence on their health benefits, they have become increasingly available in the EU, in the form of food supplements, being easily found in pharmacies, supermarkets, and specialized shops, as well as in the internet (EFSA 2015b).

### 1.4 Functional Foods Versus Bioactive Molecules: Hierarchies and Regulatory Practices

Over the years, numerous concepts and definitions have been progressively established in order to distinguish the latest advances in the field of health-related nutrition. In the first instance, an increasing number of foodstuffs present on their labels several “claims,” e.g. messages or representations, which are not mandatory under EU or national legislation, including pictorial, graphic or symbolic representations which state, suggest or imply that a food has particular characteristics (European Regulation (EC) No 1924/2006). Apart from the vitamins and minerals, including trace elements, amino acids, essential fatty acids and dietary fibers, there are other substances present in natural matrices (e.g. plants and herbal extracts) that are also able to confer nutritional or physiological benefits. However, as foods with these types of claims tend to be perceived by consumers as having superior health advantages compared with other food products, general principles and strict rules should be applied to all food claims in order to ensure a high level of protection, information, and equal conditions of competition for the food industries, as well as encouraging consumers to be aware of making choices which directly influence their total intake of individual nutrients or other substances in a way which might run counter to scientific advice. In line with this, the concept of a “health claim” was established, which refers to any claim that states, suggests or implies the existence of a relationship between a food category, a food or one of its constituents, and good health (European Regulation (EC) No 1924/2006). Further, the concept of a “health food” also deserves particular mention, defining a food product that possesses “special nutritious elements” or “special healthcare abilities,” being able
to improve health and wellbeing and/or to reduce the occurrence of disorders/diseases (Bagchi 2006).

However, the labeling of a particular food product as a health food carries several conditions, including that it should have clearly identified bioactive constituents that exert beneficial effects, upheld by proper scientific support and proofs. In addition, it must be safe and its consumption should be harmless to humans, and duly supported by toxicological studies (Bagchi 2006). Finally, if it is not possible to identify the specific bioactive components, all the beneficial effects should be clearly listed and properly supported by literature (Bagchi 2006). Then, the relevant health authority will evaluate all the methodologies used to assess the real efficacy and safety of the foods and their specific bioactive constituents in order to approve and permit their qualification/labeling as a health food (Bagchi 2006; Lupton 2009).

However, approval of a food product as a health food does not mean its qualification as “functional food.” As previously highlighted, the definition of a functional food, to a certain extent, overlaps with the health food definition but after the acceptance of a particular food product as a health food, other regulatory procedures are necessary to authorize its labeling as a “functional food” (Bagchi 2006; Lupton 2009). In both cases, and despite health claims attributed to specific foods through proper scientific assessments and proofs, not all regulatory authorities permit the free labeling of health allegations. In the EU, health claims are only permitted if the labeling includes a statement indicating the importance of a varied and balanced diet and a healthy lifestyle; the quantity of the food and pattern of consumption required to obtain the claimed beneficial effect; a statement addressed to individuals who should avoid using the food; and an appropriate warning for products that are likely to present a health risk if consumed in excess (European Regulation (EC) No 1924/2006). For example, in contrast with the United States and some European regulations, the Health Food Control Act (HFCA) in Taiwan does not allow a direct link to be made between a food bioactive ingredient and a particular disease; among other explanations, some nongovernmental Taiwanese institutions state that food health products should be evaluated as a whole, and that the use of excessive amounts of adverse ingredients in their formulation should be restricted (Arvanitoyannis & Houwelingen-Koukaliaroglou 2005; Bagchi 2006; Lupton 2009). This rule makes sense because often, it is not only a specific bioactive constituent that is responsible for the supposed health benefits but all of the consumed food constituents. Whole matrices play a more important role in maintaining the health status of consumers than a single ingredient. Currently, this rule is implemented in the US as a prerequisite for foods which carry a health claim on the label (Bagchi 2006; Jauho & Niva 2013; Lupton 2009).

In general, health foods, including functional foods, claim that their use maintains or even improves a specific health status. There are numerous chemical constituents present in the whole matrices, some of which provide a greater or lesser contribution to their biological activity (Arvanitoyannis & Houwelingen-Koukaliaroglou 2005; Bagchi 2006; Doyon & Labrecque 2008; Jauho & Niva 2013). Therefore, before promoting a special food or derived ingredient as better and healthier, it is of the utmost importance to identify all the bioactive constituents, including their mechanism of action, biochemical interactions, and other specific parameters, which allows their full recognition, guides future researches, and at the same time provides scientific evidence for their regulatory approval and ensures the correct and safe dosage. These scientific proofs are
crucial to the regulatory evaluation, and are derived from *in vitro* but mainly *in vivo* studies and clinical trials.

In respect to food consumption, claims should not be interpreted in a unidirectional manner. On one hand, there are no foods with approved health claims without proper scientific support, but on the other hand, hasty conclusions should be avoided. Bioactive molecules exist to a large extent in many food products but it is important to select foods rich in these constituents. In this way, not only the specific health benefits conferred by these selected components but also other additional effects (e.g. provided by the biochemical interactions and synergisms between the pool of chemical constituents) will be achieved (Bagchi 2006; Mukherjee & Houghton 2009; Yildiz 2010). Several experiments have shown that the most pronounced benefits are obtained by using the whole matrices rather than isolated/individual constituents.

1.5 Challenges and Opportunities: A Multidimensional Perspective

In line with current research, a multitude of health benefits provided by the consumption of plants, mushrooms, nuts, and other whole matrices have been increasingly reported and are recommended by public health guidelines (American Dietetic Association 2009; Balch 2006; Fenech *et al.* 2011; Ferguson 2009). However, despite current achievements, several problems still exist.

There are no doubts about the real potential of naturally occurring edible products, but strategies to improve their biological availability, applicability, consumption strategies, etc. are not completely established. Additionally, for the majority, the active principles, modes of action, and therapeutic properties have not been adequately determined. So, intense work is still being carried out. Different strategies need to be implemented in order to improve the applicability and potential of natural matrices and their bioactive components, including their potential for improving the nutritional and possibly therapeutic values of other food matrices (Barroso *et al.* 2014; Bigliardi & Galati 2013; Nasri *et al.* 2014; Sadaka *et al.* 2013). Microencapsulation techniques help to ensure the sustained release of active principles derived from plants, foods, and even whole matrices, in order to improve their metabolic and physiological functions and at the same time reduce the occurrence of side-effects (Barroso *et al.* 2014; Bigliardi & Galati 2013; Ribeiro *et al.* 2015; Sadaka *et al.* 2013).

Another interesting biotechnological advance in the food industry is the inclusion of plants (namely herbs and spices) in different food matrices, e.g. dairy products, such as milk derivatives (Caleja *et al.* 2015*a*, 2015*b*; Carocho *et al.* 2015*a*), biscuits, etc. (Carocho *et al.* 2014, 2015*b*) to improve their shelf-life and biological potential, making them functional foods. This also helps to reduce the use of synthetic preservatives, some of which have medium- and long-term side-effects, acting as triggers for the occurrence of numerous disorders, and which even compete with numerous active principles, reducing their bioavailability and related bioefficacy. Moreover, it is also possible to improve their digestibility and organoleptic characteristics (some are marketed as gourmet products).

These types of research are time-consuming and complex procedures, in which the results obtained are not always what was expected.
Other factors should be considered, including:

- the use of whole matrices and most effective parts (taking into consideration their origin: commercial vs wild sources)
- the use of isolated/individual chemical constituents and mixtures
- different dosages/concentrations
- initial vs final organoleptic properties
- bioavailability and incremental changes.

Therefore, detailed experiments need to be developed to assess and confirm the real in vivo, and to a lesser extent in vitro, bioactive potential of upcoming advances in the field of functional foods and nutraceuticals. Furthermore, many other natural matrices should be explored and their viability, stability, and feasibility duly analyzed in vitro, including determination of the edible parts and assessment of their mode(s) of action and related pharmacokinetic and pharmacodynamic parameters, in order to infer their subsequent in vivo application.

In short, despite all the currently available reports, the biotechnological and food technological areas still require intense research and innovation. The main goals of global research institutions are to provide more and better products to the human population, aiming to improve their health and wellbeing and, at the same time, to prevent the occurrence of diseases and disorders. However, it should never be forgotten that balanced nutrition is the key to an optimum health status.

### 1.6 Conclusion

With the current advances in the fields of basic and applied nutrition, numerous aspects have been progressively implemented to ensure an adequate level of organization, regulation, and certification of edible foods with claimed beneficial effects. Functional foods, for example, have gained particular attention not only from consumers but also biotechnological, chemical, pharmaceutical, and food industries, and also from medical and scientific communities. Nonetheless, with this increasing demand, it is crucially important to ensure the safety of the products and protection of consumers. Health claims and other nutritional and physiological attributes of plant food-derived formulations are increasingly found on food labels, although several requirements are mandatory. Thus, new interesting challenges and opportunities have opened up. Firstly investigated for their nutritional value, chemical composition, and health benefits, food products are currently being used to carry out multiple studies, varying from the molecular and genetic levels to biotechnological and industrial applications.

Due to the deepening of knowledge in this area and new perspectives arising, this is an almost infinite area of research, given the vast quantity of natural substances. Many studies can be undertaken to assess their biological potential; to discover their chemical composition and active principles responsible for observable bioactivities; to assess mechanisms of action, molecular and biochemical interactions, possible toxicity, and so on. Industrial and technological applications are also experiencing a rapid progress. For example, initially, naturally occurring foodstuffs with prestigious health benefits (functional foods) were marketed for direct consumption and increasingly privileged by consumers; then, a modified presentation was developed and industrial processes
applied to improve their biological potential and bioavailability. Currently, they are exhaustively tested and their ability to improve the nutritional value and bioactive potential of many other daily foods have been determined. Short- and medium-term studies and the obtained results from the organoleptic evaluations by consumers indicate a promising future in this area.

Although much more remains to be done, one factor is certain: nature can provide all the necessary tools to ensure the wellbeing and longevity of the human population.

References


