Perspective

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Italy's nutraceutical industry: a process and bioeconomy perspective into a key area of the global economy

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Received July 19, 2019; revised September 21, 2019; accepted September 25, 2019
View online November 9, 2019 at Wiley Online Library (wileyonlinelibrary.com);
DOI: 10.1002/bbb.2059; *Biofuels, Bioprod. Bioref.* 14:180–186 (2020)

Abstract: Focusing on the development of Italy's nutraceutical industry, one of Europe's largest, this study offers a process and bioeconomy perspective that will be useful to countries willing to establish their own national dietary supplement industry as a key industrial asset in their economies. © 2019 Society of Chemical Industry and John Wiley & Sons, Ltd

Keywords: bioeconomy; circular economy; dietary supplement; nutraceutical

Introduction

Italy's nutraceutical industry is the largest in Europe, with a 23% market share and €3.3 billion revenues in 2018, followed by Germany (13% market share), France (9%), and the UK (8%).[1]

One can read on the website of the European Nutraceutical Association that nutraceuticals 'are nutritional products that provide health and medical benefits, including the prevention and treatment of disease. In contrast to pharmaceuticals however, these are not synthetic substances or chemical compounds formulated for specific indications. These are products that contain nutrients (partly in concentrated form) and mostly are assigned to the category of food. Dietary supplements are a typical example for nutraceuticals, but also dietetic and functional foods may be counted among these products.'[2]

Even though critics emphasize that there are no internationally agreed definitions of 'nutraceuticals', 'functional foods', or 'health foods',[3] the word 'nutraceutical', coined by DeFelice, a medical doctor, in the early 1980s by merging the words 'nutrient' and 'pharmaceutical',[4] is now commonly used to refer to the 'nutritional products that provide health and medical benefits' mentioned above.

It is now commonly accepted by Italy's medical community that standardized nutraceutical products sold in packaging similar to that of drugs (pills, syrups, extracts, tablets, etc.) are important for maintaining wellness and good general health. They can balance often inappropriate lifestyles and nutritional intake, and are useful for various specific situations such as intense sport practice, pregnancy, or post-menopause. They are also beneficial in pre-pathological situations (incipient high levels of total or LDL-cholesterol), or for aging subjects with low levels of vitamin D_3.[5]

Indeed, social science scholars recently found that medical doctors or pharmacists were responsible for recommending products to 82% of Italy's nutraceutical product consumers, 57.3% of whom started to use food supplements following such suggestions.[1]

This study shows how the development of Italy's nutraceutical industry can guide other countries in establishing their own national nutraceutical industries as key industrial assets in the unfolding bioeconomy, using renewable biological resources 'to create economic activity and public benefit'.[6]

This is illustrated by the case of Stevia, a natural sweetener that has health benefits. Rapid advances in green chemistry

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technology increasingly allow the production of Stevia extracts, which lack a liquorice-like after taste, which have a high degree of chemical and physical stability, and which can be used in baked food products and beverages that are consumed on a mass scale.[7]

Industry and market

In Italy, 32 million citizens use nutraceutical dietary supplements, 18 million on a regular (daily or weekly) basis. Remarkably, most (62.8%) dietary supplement users are aged between 35 and 64 – they are of working age.[1]

When asked whether consumption of nutraceuticals had any effect on health, the overwhelming majority (74%, Fig. 1) of Italy's nutraceutical consumers responded that positive effects on health were evident. Only 1.7% of the sample complained of negative effects.[1]

Reflecting the positive effects of nutraceutical products on prevention, 58.1% of Italy's nutraceutical consumers were found to enjoy good health.

Between 2008, when revenues amounted to €1.3 billion, and 2018, when turnover increased to €3.3 billion, Italy's nutraceutical market grew by a staggering 126%.[1]

For comparison, the overall expenditure of families in Italy in the same period decreased by 0.8%. The number of workers employed by the industry (21 700) grew by 43.9% between 2014 and 2017, and revenues from nutraceutical products exported from Italy soared to €600 million (+48.5%).[1]

A list of 23 main product classes comprise the Italian nutraceuticals market, ranging from probiotics to omega-3 (Table 1).[8] Italy's nutraceutical companies are generally more profitable than equivalent small and medium enterprises

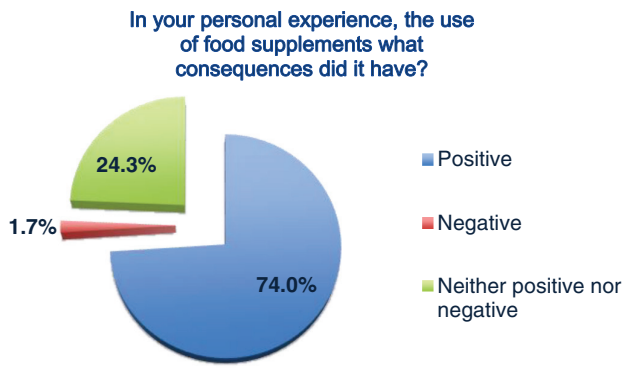

Figure 1. Survey of food supplements user experience in Italy. (Data source: Censis, 2019; reproduced from Ref. 1, with kind permission of Censis.)

Table 1. Top 10 nutraceuticals (and omega-3) sold in Italy between April 2017 and April 2018 in terms of value.

Product	Value (million €)
Probiotics	385.2
Mineral supplements	232.6
Tonics	179.2
Hypocholesterolemics based on monacolin	129.1
Multivitamin-Multimineral supplements	119.5
Intestinal function	106.3
Vitamins	103.1
Cough (suppressants, expectorants, etc.)	98.7
Joints (joint health, anti-arthritic etc.)	93.3
Sleep and calm (stress-reducing and sleep-inducing products, sedatives, etc.)	91.6
Antiacid, anti-heartburn and anti-acid reflux	88.6
Omega-3	39.6

Source: FederSalus with data from New Line Ricerche di Mercato and IRi, April 2018.

(SMEs). The return on equity (ROE) of 174 representative companies in 2017 was 18.4%, when the average ROE of Italy's SMEs slightly exceeded 11%.[9]

About €1.33 billion of the overall €3.2 billion market in 2017 is owned by Italian firms,[10] 198 of which, by late 2018, were associated with a trade organization (FederSalus) created in 1999 by 12 pioneer companies.

Another trade group, the European Nutraceutical Association (ENA), relocated its headquarter from Basel in Switzerland to Parma, Italy. The latter city hosts the headquarter of the European Food Safety Authority (EFSA) whose 'scientific opinions' are crucial to the nutraceutical industry, as they stipulate which health claims are scientifically proven and can be inserted in the labels of nutraceutical products' packaging.

In agreement with European legislation on food supplements drafted in 2002, which defined food supplements as 'foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect… designed to be taken in measured small unit quantities',[11] the industry correctly promotes the intermediate role of its products between foodstuffs and pharmaceuticals.

Nutraceuticals are neither drugs nor foodstuffs, and yet they have a specific identity, exert a specific preventive action, and have a specific role: to promote and conserve good health.

The regulatory framework for Italian food supplements is that of the European Union, with EFSA playing a central role concerning health claims.[12]

Substantiating the health benefits

Noting the absence of a shared definition of nutraceuticals, scholars have recently argued that 'the effective use of nutraceuticals in prevention and therapy' is limited by 'the lack of clinical data substantiating in full their efficacy which prevents the obtainment and use on the label of a health claim.'[13]

The industry, however, is aware of the need to support and promote an evidence-based approach. For example, in 2017, a joint industry-academy-clinical research team (the Italian Study Group on Healthy Aging by Nutraceuticals and Dietary Supplements) published the outcomes of a scientific literature search that aimed to identify the most relevant positive study for each micronutrient included in dietary supplements and nutraceuticals commercialized in Italy in each of three selected areas (bone, skeletal muscle, and cognitive function).[14]

The team found 12 relevant positive studies (one international society guidelines / recommendation, one systematic review, seven randomized controlled trials, and three prospective cohort studies), with only 16 micronutrients (beta-alanine, calcium, creatine, fluorides, leucine, magnesium, omega-3 fatty acids, potassium, vitamin B_6, vitamin B_9, vitamin B_{12}, vitamin C, vitamin D, vitamin E, vitamin K2, and zinc) supported by scientific evidence for improving musculoskeletal health and / or cognitive function in older people.[14]

Two selected nutraceutical products representing renowned and emerging nutraceuticals, omega-3 lipids and olive biophenols, show how companies are increasingly using clinical studies to substantiate claims and to provide customers with the required data supporting the health benefits that are claimed.

Numerous randomized controlled trials and extensive biochemical research show, and explain, the health benefits of omega-3 long-chain polyunsaturated fatty acid (PUFA) supplementation, overall and for brain and heart health.[15]

From time to time review studies are published stating that omega-3 supplements have little or no health benefit, for example on cardiovascular health.[16] The international trade organization for omega-3 ingredients and formulation manufacturers thus started to build a clinical study database cataloging every human clinical trial on the two main PUFAs in omega-3 lipids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The database will be available in late 2019 or early 2020.[17]

Recognizing the need to avoid industry and scientific jargon when talking to consumers about the health benefits of its products, the same organization created infographics, interactive digital guides, and visual displays covering a wide range of content on the biochemical activity of omega-3 lipids.

These tools are being used, for example, at trade events such as the one held in Switzerland that every year hosts more than 1000 exhibitors from over 100 countries, covering the entire nutraceutical supply chain, from ingredients to finished nutraceutical products.[18]

Olive biophenols, another example, are an emerging class of nutraceutical product ingredients that will also play an important role in the treatment and prevention of inflammation, and thus of numerous free-radical-mediated chronic diseases.[19]

Following the discovery of the direct extraction of olive polyphenols and hydroxytyrosol from olive mill waste water via incubation with citric acid, a US company had its health claims concerning olive polyphenol efficacy in protecting low-density lipoprotein (LDL) particles from oxidative damage validated by the EFSA.

Suggesting that to benefit from olive polyphenol's antioxidant properties a minimum of 5 mg of hydroxytyrosol and its derivatives should be consumed daily, the EFSA concluded that a cause / effect relationship exists between the consumption of olive polyphenol (standardized by the content of hydroxytyrosol and its derivatives) and protection of LDL particles.[20]

Subsequent health claims concerning cardiovascular health, joint protection, skincare, neuroprotection, and antioxidant activity, due to olive biophenol's broad spectrum anti-inflammatory activity, will require human clinical studies. Such studies are costly and, nonetheless, entirely feasible given the revenues generated by nutraceutical sales as well as through partnerships with public hospitals and universities.

For example, the €1.3 million 'NeurOliv' research project carried out in Germany has already shown that a variety of purified olive secoiridoids including oleuropein, hydroxytyrosol, and oleurosid, standardized for a 50 mg oleuropein/kg diet, restored brain adenosine triphosphate (ATP) levels in aged mice, showing evidence that a diet rich in purified olive polyphenols has positive long-term effects on the cognition and energy metabolism in the brains of aged mice.[21]

Active ingredient production

Nutraceutical manufacturers formulate both self-produced and contracted ingredients. Whereas the pharmaceutical industry mostly relies on active pharmaceutical ingredients purchased by fine chemical and active pharmaceutical ingredient (API) manufacturers, mostly located in Asia (the

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'contract manufacturing organizations'), the nutraceutical industry tends to partner with a few suppliers acting more as co-manufacturers rather than suppliers needing to undergo regular audits and certification.

Both ingredient manufacturers and finished nutraceutical manufacturers are part of the very same industry, in which synergy dominates and the success of all business partners is a common interest of the partnerships characterizing the industry.

In the course of the last decade, chemical technology for the extraction of the industry's bio-based ingredients and the preparation of finished products has evolved significantly. Examples range from marine oil PUFAs, extracted and refined with supercritical carbon dioxide extraction and chromatography ($scCO_2$),[22] through coenzyme Q10 (ubiquinone playing an important role in mitochondrial cell physiology and as a powerful antioxidant) nanostructured beadlet formulation of enhanced bioavailability.[23]

Organic chemists working in other organic process industries may find it instructive to learn how the nutraceutical industry has developed some of its advanced technologies, often in partnership with small companies, focusing on specific nutraceutical ingredients whose efficacy was recognized by regulatory authorities. Selected examples show evidence of this trend.

In Europe, one large vitamin and fine chemical manufacturer based in Switzerland was purchased in the early 2000s by a large chemical company based in the Netherlands. Besides being one of today's leading suppliers of vitamins, carotenoids, and other valued ingredients for the food, pharmaceutical, and personal care industries, the Swiss company currently markets several finished dietary supplements.

In 2008, the latter company became the major shareholder of the small enterprise, based in Great Britain, which had identified tomato extract's antiplatelet properties, developing the technology to produce a highly stable and water-soluble tomato extract (Fruitflow), which inhibits platelet aggregation.[24]

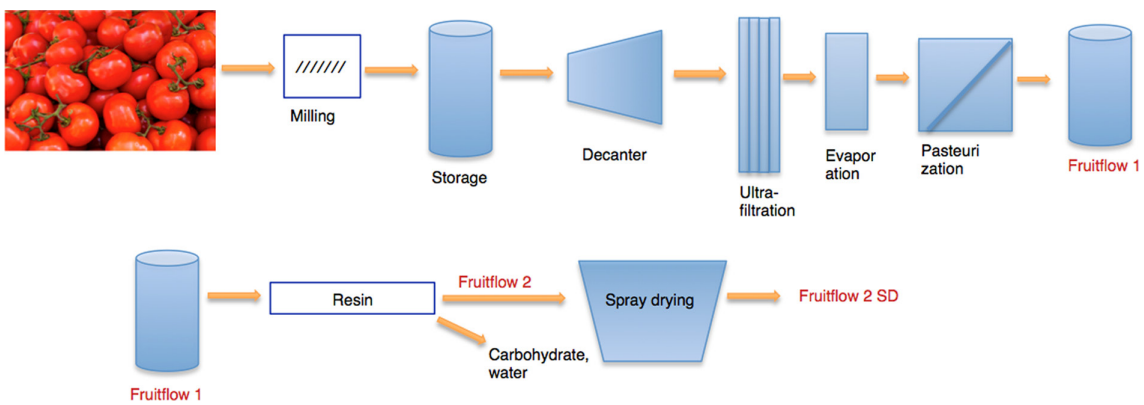
The syrup and powder versions of this extract are Generally Regarded as Safe (GRAS) in the USA and are not regarded as Novel Foods in the EU, enabling their wide use in foods, beverages, and supplements.

The extract is reproducibly produced starting from minimally processed tomato, grown and harvested under controlled conditions in a five-step process, which utilizes physical separation methods at low temperature to remove pulp and unwanted insoluble solids from the starting material followed by a brief pasteurization step to achieve the desired extract, free from microbiological contamination (Scheme 1).[25]

The clear yellow juice is concentrated by low-temperature evaporation and standardized for pH, affording a first ingredient ready to formulate nutraceutical syrups.
A carbohydrate-free product is obtained from the aforementioned clarified juice followed by removal of all carbohydrate molecules (up to 2% of the fresh weight of the tomato-derived starting material) over a resin column.

The latter components are recovered from the column. The concentrate (concentrations 28–32 times higher than in Fruitflow, due to the removal of carbohydrates and water) is dried to powder and standardized for moisture content, ready to formulate the low-calorie cardio-protective nutraceutical.[25]

Another bioactive ingredient widely used to formulate multivitamin formulas and anti-aging supplements is α-lipoic acid (1,2-dithiolan-3-pentanoic acid, also known as thioctic acid or vitamin N), a potent $OH^{\bullet}$ radical scavenger acting as a mitochondrial antioxidant agent, promoting anti-inflammatory and anti-thrombotic pathways (also beneficially influencing nitric oxide-mediated vasodilation).



Scheme 1. Production of two main Fruitflow ingredients used to formulate syrup and powder dietary supplements. (Adapted from Ref. 25, with kind permission.)

One active pharmaceutical ingredient manufacturer based in Italy produces the bioactive (*R*)-(+)-α-lipoic acid isomer by reacting the ester of *R*-(+)-dichlorooctanoic acid isolated from the racemate 6,8-dichloroctanoic acid (a chemical easily found on the market) with the optically active base (*S*)-α-methylbenzylamine, with alkali disulfide by phase transfer catalysis (Scheme 2).[26]

In the presence of a quaternary salt, such as tetrabutylammonium hydrogensulfate, the disulfide ion from the aqueous solution containing the corresponding alkali disulfide is transferred to the organic phase. High-quality (*R*)-(+)-α-lipoic acid, free of polymerization contaminants typical of previous resolution of racemic lipoic acid, is then obtained via straightforward hydrolysis of the (*R*)-(+)-α-lipoic acid ester.

Insoluble in water, and unstable against oxidation and heat-driven polymerization (with loss of its bioactivity and the formation of an unpleasant sulfurous odor), the free acid is then stabilized and made bioavailable by nutraceutical companies using proprietary techniques such as 'fast-slow' microencapsulation technology, improving its overall efficacy via rapid release of the initial 50% of the active ingredient and a slow release of the residual 50%.[27]

Driven by the same societal megatrends that are reshaping the chemical industry,[28] today's nutraceutical industry is increasingly adopting green production processes typical of the circular economy in which its bio-based ingredients are obtained from biological resources previously discarded as waste.

1. Salifying of racemic 6,8-dichlorooctanoic acid with *S*(–)α-methylbenzylamine

2. FItration of the crystallized diastereoisomeric salt of *R*(+)-6,8-dichlorooctanoic acid-*S*(–)α-methylbenzylamine

3. Purification by re-crystallization of the diastereoisomeric salt of *R*-(+)6,8-dichlorooctanoic acid-S(–)α-methylbenzylamine

4. Separation of the diastereoisomeric salt to obtain *R*-(+)6,8-dichlorooctanoic acid by reation of said salt with strong mineral acids

5. Esterification of R(+)6,8-di-halo-octanoic acid to obtain the corresponding alkyl ester

6. Reaction of the alkyl ester of *R*-(+)6,8-dichlorooctanoic acid in organic solvent with an aqueous solution of alkali disulfide in the presence of quaternary ammonium salt

7. Hydolysis of the ester of R(+)α-lipoic acid and isolation of the free acid

Scheme 2. The direct synthesis of via phase transfer catalysis transformation of the optically active ester. (Adapted from Ref. 26, with kind permission.)

For example, selected omega-3 ingredient manufacturers have started to extract fish oil from fish and crustacean processing leftovers rather than contributing to overfishing of several marine species.[22] Similarly, by sourcing olive polyphenols from olive mill waste water, nutraceutical ingredient manufacturers end a serious environmental problem, closing the production cycle and obtaining polyphenol extracts with an exceptionally high load.[29]

Several other green chemistry technologies applied to circular economy processes have been developed to produce valued ingredients for the nutraceutical, cosmetic, and personal care industries. Examples range from the use of solar energy to the extraction of valued essential oils, pectin, and polyphenols from waste orange peel,[30] and *nopal* from *Opuntia ficus-indica* cladodes,[31] through to the solvent-free microwave extraction of valued components of officinal plants.[32]

Showing further evidence of this ongoing change, a leading researcher in the fine chemical and vitamin industry (whose company supplies nutraceutical ingredients to companies across the world) noted in his 2018 account on vitamins and nutraceuticals from the perspective of process research that there were three 'general trends' concerning the large-scale preparation of vitamins, nutraceuticals, and fine chemicals: (i) the shift from stoichiometric to catalytic protocols, (ii) the shift from batch to continuous processes, and (iii) the use of bio-based raw materials in place of petroleum-derived materials to access key building blocks.[33]

For instance, the company mentioned above using coenzyme Q10 to produce its nanostructured nutraceutical, manufactures the coenzyme Q via molybdenum-catalyzed allylic substitution for the coupling of protected aromatic precursors with the C_{50} side chain of isodecaprenol obtained from tobacco-derived solanesol, developed by Netscher, Bonrath, and co-workers at the company's research laboratories.[34, 33]

Outlook and Conclusions

In the course of the last decade, the global nutraceutical industry has experienced dramatic growth. Revenue of $231 billion in 2018 is projected to grow at a 7.8% compound annual growth rate from 2018 to 2023.[35] The growth of Italy's nutraceuticals market, currently the largest in Europe, accompanied that of the rest of the world.

The case of Italy, where a large nutraceutical industry was created mostly in addition to the existing pharmaceutical

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industry, offers three main guidelines to other countries (such as Brazil, where the industry is also growing at fast pace)[36] willing to establish their own national nutraceutical industry as a key industrial asset in their overall economy.

First, nutraceutical companies need to substantiate health claims with the outcomes of clinical trials as was done, for example, with a recent randomized, double-blind study on the efficacy of a red yeast rice-based nutraceutical (monacolin K 10 mg/dose) plus probiotic (*Bifidobacterium longum* BB536) in patients with moderate hypercholesterolemia.[37]

Second, companies will increasingly adopt sustainable production and advanced packaging technologies typical of pharmaceuticals. For example, a nutraceutical company in Italy uses a product pack with a tamper-evident packaging closure showing evidence of effective closure since the purchasing ofthe product through tactile and chromatic indications.[38]

Accelerating the uptake of sustainable (zero-emission and circular) production technologies in the nutraceutical industry requires an increase in the number of university graduates with advanced knowledge and skills in the two main green chemistry industrial technologies, i.e. catalysis for synthetic organic chemistry[39] and green extraction of natural products.[30,32]

Yet, what Italy's and Europe's nutraceutical industry often face is a situation similar to that of the overall US economy where a recent survey of 600 employers carried out by a reputed education services firm found that 'anywhere there is a mismatch between the skills employers need and how students and employees are trained',[40] with the majority of employers reporting that 'recent college graduates are *not* well prepared for the workplace'.[40]

Similar findings concern many of current rapidly emerging professional fields, requiring updated knowledge and skills in today's science and technology, including biotechnology for the bioeconomy,[41] solar energy,[42] energy management,[43] and hydrogen energy.[44]

The third main guideline of this study, therefore, is that filling this gap requires the development of short-term, practice-oriented courses through which graduates who are 'not prepared for the workplace' can acquire the knowledge and practice the skills necessary to excel in the numerous jobs in the nutraceutical industry.

Many recent advances in nutraceutical science and technology – from the new green chemistry processes mentioned above to the new role of phytochemistry in the emerging bioeconomy – are ideally suited to enter the curricula of renewed chemistry courses using recent research outcomes.[45]

As the global shortage of highly skilled workers is expected to reach 38–40 million by 2020,[46] universities will find in nutraceutical science and technology a key area of the unfolding bioeconomy through which to expand and to improve their educational programs.

Acknowledgements

This article is dedicated to Professor Roberto Crea, eminent biochemistry scientist and chemistry innovator, on the occasion of his 70th birthday. Thanks to Lita Fotios for the elegant photograph, retrieved online from Pexels, used to produce the table of contents image.

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  | *Biofuels, Bioprod. Bioref.* **14**:180–186 (2020); DOI: 10.1002/bbb.2059