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Opinion

Nutraceuticals and Botanicals. Past, Present and Future

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Abstract

In this paper, the increasing influence and persistence of food supplements on the market, in particular those based on plant extracts botanicals, are considered. However, these products are in discussion at several levels, including validation and legal classification, converging in the health claim debate. Three aspects about the future of botanicals are analysed: the evolution of the products (functional foods), the utilization of adequate analytical devices (HPTLC), the new entries (bud-derivatives).

Keywords: *Food Supplements; Botanicals; HPTLC; Functional Foods*

Introduction

According to the most general definition, food supplements are "concentrated sources of nutrients with nutritional of physiological effects whose purpose of to supplement the ordinary diet", they are designed to supply nutrients, micronutrients and other physiologically active substances in predetermined amounts. "They are marketed in dose form, i.e. pills, tablets, capsules, liquids, etc. in a measured dose" [1]. The common aspect is the presence of nutrients as natural products in contrast with medicine drugs, where the presence of synthetic products is relevant and generally considered dominant in the market. In the last decades, food supplements evidenced an increasing presence in the market and consumption, but also a complex evolution that changed radically forms, targets and composition, influencing also healthy aspects.

The first key word that we are going to use is natural (products). The second one is food, considering the nutritional aspect, meaning alimentation but also health. The third one is supplement. If the ordinary food is sufficient to survey but not to maintain wellness, it is necessary to add a supplement. The result is healthy food supplements based on natural products.

In the food supplements of first generation, the composition was limited to vitamins, minerals, proteins, carbohydrates, in consideration of use mainly dietary and simple targets. Explicit goals were the intent to support nutritional needs and/or supply alimentary deficiencies derived from insufficient or inadequate input of primary substances, like the absence of essential amino acids in some vegetables or lack of vitamins in ordinary processed foods. In this case, composition in quality and quantity are well defined, as well as classification easily determined.

Later, a second generation of food supplements appeared [2], characterized by the expectation for a better live and health maintenance, with consequent contamination of the narrow border between drug and food. Their composition showed a massive introduction of secondary natural products, collectively named as "other substances", to be distinguished from the former constituents. Identities of these products (in composition, utilization, manufacture, quality control, etc.) were different from those of the first generation and several new names spontaneously appeared to mark the differences, including nutraceuticals (the most frequently used, but still not officially recognized), dietary supplements, medical devices, herbal drug preparations, traditional herbal medicine products, and others [3]. Their principal marks are: complex composition difficult to determine, multipurpose and multiaction, absence of toxic and collateral relevant side effects, possible utilization for long times. Often, a contamination between vitamins or fatty acids with botanicals is also possible.

Times are ready for the third generation of food supplements. The future invasion of the food market will see the appearance of special medical or healthy purpose foods, or simply pharmafoods, that will be followed by functional foods and multifunctional foods [4,5] (Figure 1). In this way, we started with products tailored for the pharmaceutical markets and finished with the hypermarket selling system.

The term functional food was first officially introduced in Japan in the mid-1980s, defined as FOSHU that means Foods for Specific Health Use. They are eligible to bear a seal of approval from the Japanese Ministry of Health and Welfare. Currently in Japan more that 100 products are licensed as FOSHU. So far, in Europe, the functional food category is not recognized legally.

The effectiveness of a FOSHU product on the human body is proven by several characters.

1. Absence of any safety issues (animal toxicity tests, confirmation of effects in the cases of excess intake, etc.).
2. Use of nutritionally appropriate ingredients (e.g. no excessive use of salt, etc.),
3. Guarantee of compatibility with product specifications by the time of consumption,
4. Established quality control methods, such as specifications of products and ingredients, processes, and methods of analysis. For example, dietary fibre, sugar alcohols, oligosaccharides, proteins, polyphenols, lacto- or bifido-bacilli, chitosan and sodium alginate are considered to help in maintaining good health.

The Plant Side of Food Supplements

Let us focus now on the most genuine expression of nutraceuticals, clearly connected with natural products boom. In 1989, Stephen L. DeFelice, founder and chairman of the Foundation of Innovation Medicine coined the word Nutraceutical, a portmanteau of the words "nutrition" and "pharmaceutical", with the evident intent to evidence the therapeutic nature of these products. The word is now used as a broad umbrella term to describe any product derived from several natural sources with extra health benefits. Plant natural products are the main constituents of Nutraceuticals.

Natural products from plant origin are emerging from a long period of obscurantism. Herbals have been dismissed by the mainstream of medical fraternity as plant-based quackery, even if many pharma products are themselves plant derivatives or plant containing.

Nutraceuticals reversed the pharmaceutical ostracism by the force of market numbers. According to Ikon, a market research industry, over the next five years the nutraceutical industry is expected to double (thanks to a growing healthy rate of 18.46%), also by support of the traditional pharmaceutical companies. Companies, including the giants previously focused on prescription sales, i.e. anti-infective, cardio and gastroenterology drugs, orthopedics and pain killers, and later on OTC, are now moving into nutrition, including food supplements.

Food supplements based on other substances comprehend a large number of products containing mainly natural substances derived from secondary metabolism. This category includes substances derived from algae, fungi, lichens, but plants play the principal role, giving rise to the subcategory of botanical food supplements, or simply Botanicals. Botanicals therefore contain extracts of plants obtained in several ways and marketed in different forms. They clearly relate to the herbal traditional medicine experience and the Materia Medica tradition, modified by the modern technological methods and production processes. Botanicals contain a large number of different constituent, including alkaloids, polyphenols, terpenes, and many others, depending from the utilized plant raw material. Common examples of botanicals include old and well known medicinal plants, such as ginkgo, aloe, Echinacea, garlic, ginseng, garcinia and St John's Worth, as well as several species recently introduced and without international scientific references. The introduction of several imported botanical drugs, previously unknown in the UE market, made necessary a new category, named novel food, in the EU regulation. Novel foods are "foods and food ingredients that have not been used for human consumption to a significant degree in the EU before 15 May 1997." The regulation defines novel foods as:

a. Products that have no history of "significant" consumption in the EU prior to 15 May 1997
b. Foods that result from a process that has not been previously used for food, or,
c. Foods that have undergone genetic modification and have new traits.

Similar regulations are present in other countries. Thus, in Canada the first item was changed in "that has never been used as food".

The motivation of the novel foods introduction is evident. Thanks to the globalization, many new plants have been introduced in markets of countries different in traditions, uses and regulations. For most of them scientific literature data are absent, including toxicity, or reported in local and unreliable journals.

Therefore, a food supplement is a complex matter, with many aspects to be explored and defined. The consequence is that so far, each country has a different classification and regulation, meanwhile the market experiments a special own evolution following the consumers needs. The conflict between rules and market so far is not solved.

Regulation on Food Supplements

US Regulation

Regulation in United States is directly related to Food and Drug Administration (FDA). FDA is an agency within the U.S. Department of Health and Human Services. The service of FDA is "protect the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices". The agency also is "responsible for the safety and security of nation's food supply, cosmetics, and dietary supplements, products that give off electronic radiation and for regulating tobacco products". For long time FDA assigned to products similar to EU food supplements the unique category of dietary supplements.

The Dietary Supplement Health and Education Act (DSHEA) of 1994 [7] placed dietary supplements in a special category under the general umbrella of foods, assigning not drugs pertinence and requiring that every supplement be labelled as dietary supplement.

More precisely a dietary supplement is a product taken by mouth that contains a dietary ingredient intended to supplement the diet. The dietary ingredients in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandular and metabolites. Dietary supplements can also be extracts or concentrates that may be found in many forms, such as tablets, capsules, softgels, gelcaps, liquids or powders. Dietary supplements can also take other forms, such as a bar. If they do, information on their label must not represent the product as a conventional food or a sole item of a meal or diet.

In 2006, a new category was introduced to specify the botanical products tailored for a medical target. Products of the new category were named botanical drugs. Therefore, a botanical drug product is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans. Raw materials of a botanical drug product consist of botanical or related materials, which may include plant materials, algae, macroscopic fungi, or combinations thereof. A botanical drug product may be available as (but not limited to) a solution (e.g., tea), powder, tablet, capsule, elixir, topical, or injection. Botanical drug products often have unique features, for example, complex mixtures, lack of a distinct active ingredient, and substantial prior human use. Therefore, a botanical drug product can derived from one or more plant materials with varying degrees of purification. Fermentation products and highly purified or chemically modified botanical substances are not considered botanical drug products.

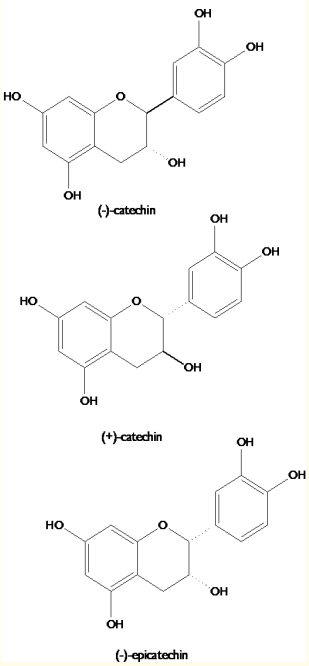
Just as for other types of drugs, the safety and efficacy of a botanical product are established through clinical trials. In addition, manufacturers of a botanical drug product must ensure rigorous control of raw materials, and good agricultural and collection practices, together with analytical testing of the complex mixture.

So far, only two botanical drugs were admitted by FDA: Veregen®, approved in 2006, and Fulyzaq®, approved the 31 of December 2012.

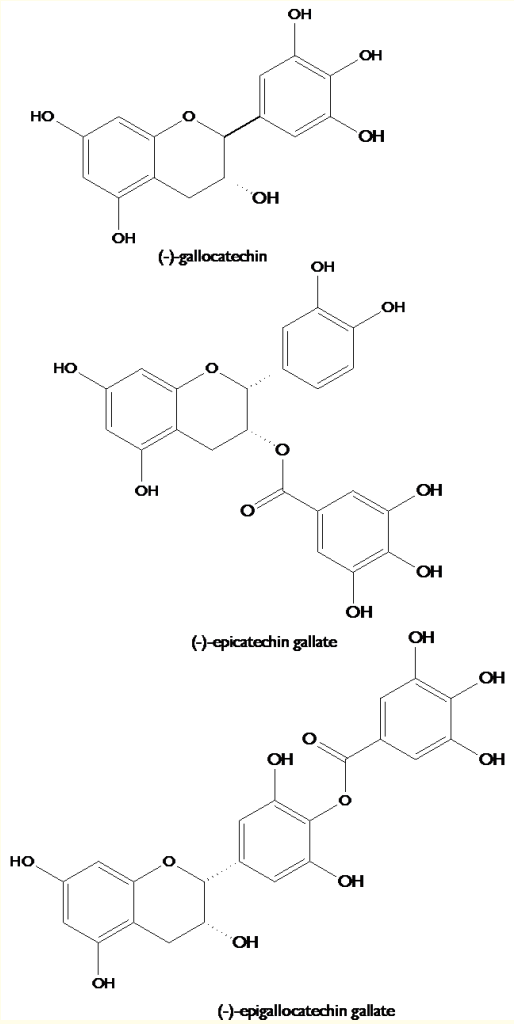
Veregen® (sinecatechins) Ointment is a botanical drug product for topical use. The main drug constituent in Veregen® is sinecatechins, which is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis*. Chemically, Veregen® is a mixture of catechins and other green tea components. Catechins constitute 85 to 95% (by weight) of the total drug substance which

includes more than 55% of Epigallocatechin gallate (EGCg), other catechin derivatives such as Epicatechin (EC), Epigallocatechin (EGC), Epicatechin gallate (ECg), and some additional minor catechin derivatives i.e. Gallocatechin gallate (GCg), Gallocatechin (GC), Catechin gallate (Cg), and Catechin (C). In addition to the known catechin components, it also contains gallic acid, caffeine, and theobromine together playing about 2.5% of the drug substance. The remaining amount of the drug substance contains undefined constituents. In 2006, the FDA approved Veregen as the first botanical prescription drug for external treatment of genital and perianal warts.

The second approved product was Fulyzaq (crofelemer) to relieve symptoms of diarrhoea, for treatments including HIV/AIDS patients taking antiretroviral therapy, a combination of medicines used to treat HIV infection. Diarrhoea is experienced by many HIV/AIDS patients and is a common reason why patients discontinue or switch their antiretroviral therapies. Fulyzaq is intended to be used in HIV/AIDS patients whose diarrhoea is not caused by an infection from a virus, bacteria, or parasites. Patients take Fulyzaq two times a day to manage watery diarrhoea due to the secretion of electrolytes and water in the gastrointestinal tract.



Fulyzaq derived from the red sap of the *Croton lechleri*. The plant is the most famous of several species present in Central countries of South America, producing a red sap well known and widely used in Peruvian traditional medicine. The sap is called sangre de drago for the characteristic strong red colour, albeit other Croton and allied species are currently used. The safety and efficacy of Fulyzaq were established in a clinical trial of 374 HIV-positive patients on stable antiretroviral therapy with a history of diarrhoea lasting one month or longer. The median number of daily watery bowel movements was 2.5 per day. Patients were randomly assigned to take Fulyzaq or a placebo twice daily. The trial was designed to measure clinical response, defined as the number of patients who had two or fewer watery bowel movements weekly. Results showed that 17.6% of patients taking Fulyzaq experienced clinical response compared with 8% taking placebo. In some patients, a persistent anti-diarrhoeal effect was seen for 20 weeks. Common side effects reported in patients taking Fulyzaq in the clinical trial were upper respiratory tract infection, bronchitis, cough, flatulence, and increased levels of the liver enzyme bilirubin.



EU Regulation

Among the EU regulatory agencies, a matter of concern is the evaluation of popular medicine indications in the claim validation. We already found the introduction of the concept about history of "significant" consumption, consistent in the "familiarity" of the substance; but we need to understand what is significant or not.

The EMA, European Medicines Agency (formerly known as EMEA, European Agency for the Evaluation of Medicinal Products) consider positively the documented use of the ingredient from at least 30 years, including the popular utilization. On the contrary, EFSA (European Food Safety Authority) so far did not accept any documentation about traditional uses. Everybody understands that this is crucial for botanicals, directly derived from the traditional medicine.

So far, EFSA gave negative opinion to most of health claims for "other substances" on the basis of not adequate or sufficient scientific evidences, using the same level of judgement used for medicinal drugs. The opinions were assessed also for substances/products that have been legally sold with health claims in national markets for many years, without being challenged under national legislation. However, these opinions were without any real effects, considering that 95% of all health claims for "other substances", like botanicals,

should be prohibited when the legal decision should be adopted. The expected consequences could be a decrease of the food supplements market by about 25% (645 million euro) and 30% loss of gross profitability (242 million euro), followed by 18% of total employment in a sector that was the only one registering a positive trend in the pharmaceutical market [8]. Considering that Europe is facing a long economic crisis, the situation became a cul-de-sac, the EFSA refusing to change its negative attitude without any consideration of real consequences. The impasse can be solved only changing the relative positions. Nutraceutical industry must invest part of the money accumulated in these years in the necessary validation and research; but criteria for health claims consideration must changed and adapted to the nature of Nutraceuticals and botanicals.

Looking for the Future

The trajectory of botanicals seems not near to end. Several clues are useful to understand the future steps. Among the peculiarities of botanicals, the reversal of dominant paradigms to open the door to novelties. Three aspects were selected: the evolution of the products (functional foods), the utilization of adequate analytical devices (HPTLC), the new entries (bud-derivatives).

Functional foods

Addition or changes of ordinary foods will increase, as a consequence of the health maintenance demand. Also in this case, the differences are difficult to sign. In 1994, the Institute of Medicine's Food and Nutritional Board (USA) defined functional foods as "any food or food ingredient that may provide a health benefit beyond the traditional nutrients is contains". That means that a functional food is a processed food containing specific ingredients that aid specific physiological functions in additions to the nutritional effects. In practice, we found that exactly the same definition can be applied to any kind of food supplements or dietary products. Therefore, the implemented of the definition was proposed as "in defined quantitative and qualitative amounts (functional food) provides a clinically proven and documented health benefit, and thus, an important source in the prevention, management and treatment of chronic diseases of the modern age" [9].

The difference between functional foods and the food supplements can be found in the form that the first ones clearly maintains the food form, against the tendency of nutraceuticals that mimetic the pharmaceutical one.

The explosion of consumer interest for health conditions and conscientiousness of the role of alimentation in mitigate and prevented diseases are pushing functional foods, as a leading trend in the US food industry and a potential market in Europe and China. The Decision Resources Inc. estimated at US$ 28.9 billion the global market of functional foods.

So far, we can consider functional foods basically as ordinary foods modified by addition of ingredients with specific physiological effects. Following this tendency, the terminology in the sector is never ending and other words are emerging like pharmafoods and super foods.

Let us consider one example of functional food. Chocolate is a better carrier than dairy products for intestine delivery of useful bacteria, because survival rates were found four times higher than milk consuming products. A study showed that probiotic strain *Bacillus indicus* HU36 combined with maltodestrin and lemon fiber in dark chocolate demonstrated high probiotic survival rates (up to 91%) and did not present adverse taste, color and texture. Therefore, the findings could lead to a new type of digestive health probiotic dark chocolate. The marketing operation is evident: in one product, we have alimentation, health promotion and reduction of health care cost. This is not so surprising if we consider that nutrition derives from the original Lain word that means feeding in any respect, and that really our health depends meanly by the quality of food.

Considering the composition, functional foods can be divided into mono- and multifunctional foods. In the second case, the consequence is a multi-ingredient product, which in botanicals means the mix of several plant extracts. This multiplies the difficulties in the quality control that can be obtained only by the adequate chemical analysis.

Analytical devices

On the analytical point of view, the complex composition of a plant extract is a real challenge. Most of analytical devices are born in the period of single molecule based drug and they are focused in analysis on chemically structurally defined molecules. The situation of a phytocomplex is on the opposite side. In a plant extract there are at least hundreds of constituents, and each of them could be responsible in part of an activity or co-active in some properties. The need of an analytical approach, as far as possible, complete is therefore necessary.

Recently, the capacity of Thin Layer Chromatography (TLC), the old classic and most used and useful tool in analytical separation, was highly advanced by the introduction of new material in the silica gel stationary phase of the plate, joined with several devices to automatize any step of the analysis, giving rise to a revolution named HPTLC. HPTLC is the last evolution of planar chromatography, specifically tailored for analysis of complex mixtures in order to evidence most of the constituents of an extract in an identifying track, named fingerprint [10-12]. The molecular fingerprint evidences the metabolic production typical of the plant, being the metabolic production one of the distinctive character of a species. In this way, the complexity of the solution, so far considered a disturbance by the analyst, is converted into an advance. Plates can be visualized and derivatized in several ways, obtaining multiple information. The adequate use of HPTLC is crucial since plant species pertaining to the same genus use to contain the same principal constituents and therefore this is advancement regards the analytic approach present in many monographies of Pharmacopoeias. These plant monographies are usually based on analysis restricted to one constituent representative of a class of natural products, not considering that similar species contains similar constituents [13-14].

In this way, for example, it is possible to verify the presence (or absence) of a plant in the composition of a botanical [15-18] or the addiction of a synthetic product to enhance its activity [19-20]. If the analysis of a single extract is a difficult job, the situation is very complicated when botanicals are derived from the utilization of several plant extracts. Uses of herbs in traditional medicines, derived from historical references and empirical evidences, are based on multi-ingredient preparations expressing the in toto activity of the herbal drug mixture. The analytic challenge is highly increased in case of multi-ingredient botanicals, but also in this case, the HPTLC analysis can be useful. Considering that an extract can be identified on the basis of its fingerprint, the fingerprint of each species reported in the label can be obtained, as individual track of the corresponding extract and therefore the fingerprint of the mixture of the extracts also obtained. All tracks, including that of the mixture, can be now compared with that of the analyzed product. A part from quantitative differences, the fingerprint of the mixture made in laboratory and that of the product result is very similar [21].

The new entries

Actually, the food supplements front is advancing, being completed and enriched by the micro-organisms troops concerning probiotics, the symbiotic bacteria, and prebiotics, the products useful for their health and survival, and also the appearance of emerging products, the like bud-derivatives. In particular, bud-derivatives present several novelties and special characters in comparison with the other abovementioned products. They are all coherent with the plant used part consisting not only on buds, but in any part of the plant containing meristematic or juvenile cells. A parallel has been used meristems and the animal staminal cells, although there are several differences, like the distribution in the organism, the nature of the cells, the totipotence, and the possibility to be always active. Bud-therapy has a recent story in the treatment of several health problems, although juvenile plant materials have been always used by mankind. One of the main arguments against the bud-therapy is based on their simple chemical composition, mainly based on hormones, proteins, amino acids and sugars, therefore, common to each plant. On the contrary, the HPTLC analysis showed in bud-derivatives the presence of secondary natural products and their presence in accordance with the specific metabolome [16]. Also in this case like the for other botanicals, scientific validation can be considered not adequate, depending from the level of the request.

Conclusions

The multibillion industries of food supplements is asked to replay rapidly to the current challenge, using the part of the money so far accumulated in validation and research, that means in defence of their products and relative health claims. On the contrary, the regulatory authorities are requested to change partially the health claim requirements to be adapted to the food supplements characters. Otherwise, it is possible that the liberty so far conceded will be not further allowed.

Bibliography

1. UE Directive 2002 – 2002/46/CE.
2. SANCO, Directorate General (2007) European Commission the Use of Substances with Nutritional Effect other then Vitamins and Minerals in Food Supplements. Study undertaken for European Advisory Services (EAS).
3. Nicoletti M. "Nutraceuticals and botanicals: overview and perspectives". *International Journal of Food Sciences and Nutrition* 63.S1 (2012): 2-6.
4. Hardy G. "Nutraceuticals and functional foods: introduction and meaning". *Nutrition* 16.7-8 (2000): 688-689.
5. El Schaimy. "Functional Foods and Nutraceuticals - Modern Approach". *World Applied Sciences Journal* 20.5 (2012): 691-708.
6. REGULATION (EC) No 258/97 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 January 1997 concerning novel foods and novel food ingredients.
7. DHSEA. "Dietary Supplement Education Acta (USA) on food supplements" (1994).
8. Brookes Graham. "Economic Impact Assessment of the European Union (EU)'s Nutrition & Health Claims Regulation on the EU food supplements sector and market, for the European Health Claims Alliance EHCA" (2010).
9. 9th International Conference on "Functional Foods and Chronic Diseases: Science and technology (2011)
10. Nicoletti M., *et al*. "The modern analytical determination of Botanicals and similar novel natural products by the HPTLC Fingerprint approach". In Studies in Natural Products Chemistry; Atta-ur-Rahman, Ed.; Elsevier: Oxford, UK, (2012): 217-258.
11. M Nicoletti. "Phytochemical Techniques in Complex Botanicals. The XXI Century Analytical Technique". *Journal Chromatograph Separation Techniques* 4: 186.
12. M Nicoletti., *et al*. "Fingerprint HPTLC Analysis of marketed products". *Pharmacology online* 3.6 (2013): 30-36.
13. Piccin A., *et al*. "Analytical tools for digestive plant extracts". *Nutrafoods* 11.1 (2012): 29-35.
14. C Toniolo., *et al*. "Determination by HPTLC of chemical composition variability in raw material used in botanicals". *Natural Products Research* 28.2 (2014): 119-126.
15. C Toniolo., *et al*. "The HPTLC approach to metabolomic determination of neem products composition". *Pharmacology online* 3 (2013): 123-127.
16. FR Gallo., *et al*. "Henna through the centuries: a quick HPTLC analysis proposal to check henna identity". *Brazilian Journal Pharmacognosy* 24.2 (2014): 133-140.
17. FR Gallo., *et al*. "Chemical fingerprinting of Equisetum arvense L. using HPTLC densitometry and HPLC". *Natural Product Research* 25.13 (2011): 1261-1270.
18. Nicoletti M., *et al*. "Neem cake: chemical composition and larvicidal activity on Asian tiger mosquito". *Parasitology Research* 111.1 (2012): 205-213.
19. Nicoletti, M. "HPTLC fingerprint: A modern approach for the analytical determination of botanicals". *Brazilian Journal of Pharmacognsosy* 21 (2011): 818-823.
20. Nicoletti M. "Identification of Thiosildenafil in a Health Supplement". *Natural Product Communications* 6.7 (2011): 1003-1005.
21. Nicoletti M., *et al*. "Traceability in multi-ingredient botanicals by HPTLC fingerprint approach". *Journal of Planar Chromatography* 26.3 (2013): 243-247.
22. Venditti A., *et al*. "A new problem. Contamination of Botanicals by phtalates. Rapid detection test". *Natural Product Research* 28.2 (2014): 134-137
23. Nicoletti M and Toniolo C. "HPTLC Fingerprint Analysis of Plant Staminal Cell Products". *Journal Chemical Separation Techniques* 3 (2012): 7-11.

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