



A Brief Review on the Growing Concept of Nutraceuticals

While all agree that the term “nutraceutical” comes from the association of the words nutrition and pharmaceuticals, it was actually coined in 1989 by Stephen DeFelice, MD, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, NJ.¹ According to DeFelice, any food or part of food that would provide health benefits or prevent and even treat any disease, mainly chronic ones, would be termed nutraceutical. Since then, the word became commonly used to include any food, plants, herbs, vitamins, minerals, proteins or other ingredients like pre- or probiotics, that would have the aforementioned benefits by targeting a substance insufficiency in the body or by simply supplementing and increasing the total daily intake of a constituent, metabolite, extract or the combination of these ingredients.² However, although nutraceuticals would become largely regulated by the different health bodies in various countries like the US Food and Drug Administration, European Food Safety Authority (EFSA), the Chinese SFDA, the Indian FSSAI and others, the word nutraceutical remains with no regulation definition.³

REGULATORY FRAMEWORK

For nutraceuticals manufactured by European nutraceutical companies, the manufacturing, marketing and selling of end products are mainly overseen by the EFSA,⁴ which also evaluates the claims associated with these products through the Register of Nutrition and Health Claims.⁵ Through its focal points, the EFSA cooperates with national food safety authorities that give EFSA strategic advice on scientific issues relating to nutraceuticals and food supplements and are the most important contributors of experts to EFSA. For Malta, the national regulator is the Maltese Competition and Consumer Affairs Authority.⁶ Inclusion of a new claim would require further detailed scientific testing done by the manufacturer and reviewed by EFSA. Since the health claims on product labels need to be approved by EFSA, this gives increased credibility to EU produced food supplements and nutraceuticals.⁷

SIZE OF MARKET

Despite the tough EU regulations on nutraceuticals, these didn't negatively affect the growth of the nutraceuticals market worldwide. Indeed, and as per the Euromonitor

2010 figures, it was projected that the value of the annual global nutraceuticals market would reach US\$250 billion by 2018 with the global nutraceuticals market by country/regional share split being as follows: Europe 14%, Japan 22%, USA 30% and the rest of the World 34%.⁸ In fact, the actual 2018 market size of nutraceuticals accounted for US\$379 billion with an expected large growth to reach US\$734 billion in 2026.⁹

While until recently it was perceived that pharmaceuticals are mostly medications used to treat diseases, and nutraceuticals substances used to prevent diseases,¹⁰ this distinction between pharmaceuticals and nutraceuticals has been shown to be incorrect and even erroneous.

Pharmaceuticals are compounds which undergo thorough testing. The results form part of a dossier which is evaluated by regulatory authorities and if authorised, the pharmaceutical company benefits from patent protection for that product. Though not considered strictly pharmaceutical, herbal medicinal products are also regulated products. Herbal medicinal products are either granted marketing authorization with a well-established use or are registered as a traditional herbal medicinal product. Safety and efficacy data is mandatory and is derived from bibliographic data or tests carried out by the manufacturer. On the other hand nutraceuticals do not need the same extent of testing.⁴

EFFICACY AND SAFETY OF NUTRACEUTICALS

Currently, nutraceuticals are receiving a lot of interest due to their therapeutic promises that are being increasingly documented through clinical studies and more so due to their relatively better safety profile in comparison to pharmaceuticals. However one must add that there are specific natural products that have a very narrow therapeutic window. In this case, the safety issue is linked to the long-standing use of these products with respect to pharmaceuticals.

Nutraceutical and pharmaceutical companies are aware of the increased interest by the general population in nutraceuticals due to the benefits associated with them. Whenever used for an insufficiency or deficiency in a

vitamin, mineral or other vital molecule, most nutraceuticals also possess multiple therapeutic benefits apart from their disease prevention properties.¹¹

To illustrate the importance of this relatively new healthcare industry, international exhibitions and fairs are held to allow exhibitors, mainly nutraceuticals and food supplements companies, to show the benefits of their products. Visitors of these fora include healthcare professionals from different backgrounds as well as other professionals interested in the development and growth of the nutraceutical business. Vitafoods Europe is one of the most prominent annual event where the nutraceutical industry comes together to innovate, connect with business leaders and find effective solutions in the sole interest of the individual's health. In 2019 Vitafoods gathered more than 1,250 exhibitors, 25,000 visitors and had over 110 participating countries.¹²

The list of nutraceuticals is constantly shaping up. Products, molecules and ingredients are being added or changed incessantly according to the needs of the growing market, opinion of healthcare professionals, feedback from consumers and results on efficacy and safety from ongoing researches. The safety of these products stem from the results of research and clinical trials.¹³

Nutraceuticals are believed to be effective against a plethora of diseases and disorders e.g. cardiovascular, obesity, diabetes, cancer, stress, mental and neurological diseases, hormonal disturbances, women's health disorders, respiratory disorders; they may also function as immuno-modulators, e.g. probiotics.¹³ While the mechanism of action of nutraceuticals is not fully understood, it is postulated that they are involved in a wide variety of biological processes, including the activation of signal transduction pathways, gene expression, cell proliferation, differentiation and preservation of mitochondrial integrity, and proliferation of human hematopoietic precursors. Working as antioxidants and improving antioxidant defenses is a widely accepted way of action given that reactive oxygen species and oxidative stress are more and more implicated in the etiology of many diseases including atherosclerosis, other cardiovascular diseases and cancer.^{10,13}



MANUFACTURING AND IMPORTANCE OF FORMULATION

The manufacturing process poses various challenges, including *stability testing*. The formulation used for specific minerals or ingredients, strains of probiotics and the right mixing of compatible ingredients that would not antagonize each other or decrease their bioavailability or stability are all important considerations.

The importance of the *formulation* development of two commonly available minerals, iron and magnesium, is illustrated below. Because of their low solubility, iron and magnesium are poorly absorbed from the intestine. To enhance their bioavailability, ascorbic acid may be included. While companies offer different nutraceuticals claiming to be superior in managing a condition without any side-effects, studies have shown that specific formulations ensure the best bioavailability, hence efficacy, with the least side-effects. One such formulation is the bisglycinate chelate which is made of two molecules of glycine that are chelated to mineral salts such as iron or magnesium. The mineral-bisglycinate complex is hence readily absorbed in the gastrointestinal tract without being affected by gastric or intestinal pH. It is also minimally affected by the concomitant use of other minerals, and food intake including phytic acid-rich food, thus mimicking the absorption of amino acids from the gut.¹⁴⁻¹⁶

Like with other bisglycinate minerals, magnesium has been shown to have a better bioavailability than other forms of magnesium especially magnesium oxide.¹⁷ The chelate forms of minerals are reported to have the highest absorption and bioavailability making it one of the most efficacious forms for supplementation (Table 1).¹⁸

Table 1: Benefits of the mineral-bisglycinate complex¹⁸

Characteristic of the molecular complex	Physiological significance
Stability (even in the stomach)	Lower interaction with food absorption inhibitors like phytates and oxalates; less interaction with other nutrients
Absence of electric charge (neutral molecule). The glycine molecules wrap the mineral)	Fewer gastro-intestinal side-effects because of lack of dissociation of the mineral; increased tolerability and safety
Smaller molecular size	No need for digestive processes prior to absorption; intact absorption through intestinal epithelial cells



What about the right recipe? When mixing multiple ingredients in a tablet, capsule or any other form, these must be compatible. Nutrients can be ingested as coated tablets, soft gels, capsules, sachets, effervescent tablets, chewables, dissolvable films, nutrition bars, etc. While some minerals like calcium are best delivered in tablet form, co-enzyme Q10 or lycopene are best preserved when delivered in a soft gel capsule. In the latter case their bioavailability is significantly improved since liquid matrix ingredients are designed to solubilize rapidly even for poorly soluble molecules.^{19,20}

Incompatibility of products mixed together not only may lead to physical instability of the formulation like discoloration, breaking, and formation of lumps, but also antagonism among active ingredients or simply not have the required synergistic effect. A good example of mixing compatible ingredients is the case of vitamin K₂ - also known as menaquinone - and vitamin D. This combination is used to help maintain healthy bones. These two products exert synergistic effects on bone metabolism. Vitamin D, also known as 1,25(OH) D₃ is known to promote expression, transcription and translation of osteocalcin (OC) gene. OC is secreted by osteoblasts and activated OC binds to calcium ions and hydroxyapatite crystals allowing good bone mineralization.²¹ On another hand, vitamin K₂ stimulates Matrix Gla protein (MGP), an extensively studied extrahepatic Gla protein that is synthesized by chondrocytes and vascular smooth muscle cells. Findings in both animal and human studies suggest that after being carboxylated, hence activated, MGP inhibits the calcification of arteries and cartilage, while facilitating normal bone metabolism.²² This finding has been translated clinically into improved aortic and carotid elasticity that could be explained by a reduced vascular calcification following long term vitamin K₂ administration to post-menopausal women.²³

Finally, this fast growing non-pharmaceuticals sector is witnessing better acceptance from consumers as well as healthcare professionals. All this is based on stricter manufacturing requirements like ISO standards and GMP certification (currently this is voluntary), better knowledge about the mode of action of nutraceuticals, and finally more clinical research that shows efficacy and safety.

REFERENCES

1. Brower V. Nutraceuticals: poised for a healthy slice of the healthcare market? *Nat Biotechnol* 1998;16:728-731.
2. Nasri H, Baradaran A, Shirzad H et al. New Concepts in Nutraceuticals as Alternative for Pharmaceuticals. *Int J Prev Med* 2014;5(12):1487-1499.
3. Zeisel SH. Regulation of "Nutraceuticals." *Science* 1999;285:185-186
4. The European Food Safety Authority EFSA website: <http://www.efsa.europa.eu/en/search/site/food%20supplements>. [accessed on 29-08-2019]
5. EU Register on nutrition and health claim http://ec.europa.eu/food/safety/labelling_nutrition/claims/register/public/?event=search. [accessed on 27-09-2019]
6. Focal Point Members and Observers. The EFSA website <https://www.efsa.europa.eu/en/people/fpmembers>. [accessed on 29-08-2019]
7. Permitted nutrition claims and their conditions of use. EU Register of nutrition and health claims made on foods. [accessed on 29-08-2019] https://ec.europa.eu/food/safety/labelling_nutrition/claims/register/public/?event=register.home [accessed on 29-08-2019]
8. Sterling C and Kruh W. Nutraceuticals: The future of intelligent food. Where food and pharmaceuticals converge. 2015 KPMG International Cooperative.
9. Wood L. Global Nutraceuticals Market Report. Research and Markets, Globe Newswire 2019. <https://www.globenewswire.com/news-release/2019/01/29/1706747/0/en/Global-Nutraceuticals-Market-Report-2018-Market-Accounted-for-379-06-Billion-in-2017-and-Expected-to-Reach-734-60-Billion-by-2026.html>. [accessed on 26-09-2019]
10. Zhao J. Nutraceuticals, Nutritional Therapy, Phytonutrients, and Phytotherapy for Improvement of Human Health: A Perspective on Plant Biotechnology Application. *Recent Patents on Biotechnology* 2007;1,75-97.
11. Kalra EK. Nutraceutical - Definition and introduction. *AAPS Pharm Sci* 2003;5(3):E25
12. www.vitafoods.eu.com [accessed on 30-08-2019]
13. Keservani R, Kesharwani RK, Sharma A Et al. Nutraceutical Formulations and Challenges Developing New Functional Food and Nutraceutical Products. Chapter 9:163-171. Elsevier Inc 2017.
14. Pineda O and Ashmead HD. Effectiveness of Treatment of Iron-Deficiency Anemia in Infants and Young Children with Ferrous Bis-glycinate Chelate. *Nutrition* 2001;17:381-384.
15. Hallberg L, Brune M, Eriandsson M. Calcium effect of different amounts on non-heme and heme-iron absorption in humans. *Am J Clin Nutr* 1991;53:112.
16. Gilooly M, Bothwell TH, Torrance JD. The effects of organic acids, phytates, and polyphenols on the absorption of iron from vegetables. *Br J Nutr* 1983;49:331.
17. Schuette SA, Lashner BA, Janghorbani M. Bioavailability of magnesium diglycinate vs magnesium oxide in patients with ileal resection. *J Parenter Enteral Nutr* 1994;18(5):430-5.
18. Cook S. Chelated Minerals. Addressing Key Challenges in Mineral Supplementation. *Natural Medicine Journal. Research Guide*. 2018 IMPACT Health Media, Inc: 1-7 <https://www.naturalmedicinejournal.com/journal/2019-07/addressing-challenge-mineral-supplementation-clinical-practice>. Accessed 04-09-2019
19. Moloughney S. Editor. Special Delivery: Form = Function. Innovation in dosage forms allows manufacturers to tailor products to consumer preferences. *Nutraceuticals World* 2013. https://www.nutraceuticalsworld.com/issues/2013-09/view_features/special-delivery-form-function. Accessed 05-09-2019
20. Benza HI and Munyendo WLL. A Review of Progress and Challenges in Soft Gelatin Capsules Formulations for Oral Administration. *International Journal of Pharmaceutical Sciences Review and Research* 2011;10(1):20-24.
21. Akbari S and Rasouli-Ghahroudi AA. Vitamin K and Bone Metabolism: A Review of the Latest Evidence in Preclinical Studies. *BioMed Research International* Volume 2018, Article ID 4629383, 8 pages. <https://doi.org/10.1155/2018/4629383>
22. T. Krueger, R. Westenfeld, M. Ketteler et al. "Vitamin K deficiency in CKD patients: a modifiable risk factor for vascular calcification?" *Kidney International* 2019;76,(1):18-22.
23. Knapen MH, Braam LA, Drummen NE et al. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women. A double-blind randomised clinical trial. *Thromb Haemost* 2015;113(5):1135-44.

