Evidence-Based Approach and Standardization of Nutraceuticals

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Abstract **—Evidence-based approach for the use and selection of nutraceuticals are presented as well as the need and challenges to creating a method for the standardization of these products. A systematic review was completed to analyze the impact of evidence-based and standardization of nutraceuticals. Evidence-based approach for nutraceuticals allow for the evaluation of these products. This process involves utilizing current and best evidence to provide individualized care for patients. Current Good Manufacturing Practices (cGMP) are regulations enforced by the FDA to ensure that drug manufacturing processes meet basic standards. Under these practices, design, monitoring, and control of manufacturing processes are regulated. These practices can track and provide tools to prevent contamination of products available to consumers. Using evidence-based approach for nutraceutical can provide healthcare providers and consumers with evidence that is patient specific, for a given intervention and desired outcome. The global market for nutraceuticals is growing and all manufacturers should comply with cGMP to ensure safe, quality products for consumers. The goal is to have all nutraceutical manufacturers worldwide embrace cGMP in order to provide consumers with safe, effective and high quality products.**

Keywords: Nutraceuticals, evidence-based medicine, standardization, evidence-based approach, Current Good Manufacturing Practices, FDA

Dr. Lockwood defines a nutraceutical as "the term used to describe a medicinal or nutritional component that includes a food, plant, or naturally occurring material, which may have been purified or concentrated, and that is used for the improvement of health, by preventing or treating a disease[1]." This includes anything from dietary supplements used for weight loss to herbal supplements and vitamins. Evidence-based medicine (EBM) is the use of the best, current available scientific research to make informed decisions about patient care. EBM integrates clinical expertise with evidence-based research and patient specific factors. The purpose of this study was to present evidence-based approaches for the use and selection of nutraceuticals as well as the need and challenges to creating a method for the standardization of these products. A systematic literature review was completed to analyze the impact of evidence-based approach to nutraceuticals and standardization of the regulatory process of nutraceuticals.

Dr. Hasnain-Wynia Romana states that EBM is the use of evidence that can allow clinicians to draw upon the objective experience of researchers working through scientific standards, improve efficiency of providers, decrease the use of ineffective clinical practices, aid in informing patients and clinicians by offering collectively agreed upon and publicly available information about treatment options and lastly provide a scientific basis for the construction of health care policy[2].

Izzo, Raffaele et al investigated whether addition of nutraceuticals to lifestyle management including diet counseling improved lipid profile and reduced cardiovascular risk and prevalence of metabolic syndrome[3].

One thousand, three hundred and eighty, 18 to 80 year-old non-diabetic participants with dyslipidemia, with or without metabolic syndrome not requiring pharmacological therapy were assigned to a specific diet; after 2 weeks, 690 patients were also given a nutraceutical combination over another 8 weeks[3].

Patients receiving nutraceuticals were older and more dyslipidemic than the placebo group, with no difference in other cardiovascular risk factors and prevalence of metabolic syndrome. After 8 weeks, high-density lipoprotein (HDL) cholesterol was increased and diastolic blood pressure, waist girth, triglycerides, total and non-HDL cholesterol were significantly reduced in the nutraceutical group than in the placebo group. However, systolic blood pressure and fasting glucose did not change[2]. Prevalence of metabolic syndrome was also significantly lower in the nutraceutical group (36.1%) than in the placebo group (48.1%, $P < 0.05$) and a reduction in the Framingham Risk Score, which calculates ten-year risk of coronary heart disease, of 73.3 vs. 52%, respectively ($P < 0.0001$)[3].

Their study concluded that in their large clinical sample of patients with moderate cardiovascular risk, combination of nutraceutical with dietary counseling reduced central obesity, improved lipid profile, diastolic blood pressure and Framingham Risk Score, and decreased prevalence of metabolic syndrome[3].

Khera et al measured the effect of niacin on HDL functionality but concluded niacin failed to improve clinical outcomes when adjunct to standard LDL cholesterol targeted therapy, such as statins, despite a significant increase in HDL-C levels[4].

DOI: 10.5176/2345-7201_1.1.16

Carol P. Wilson et al investigated whether or not riboflavin would be effective in lowering blood pressure when added to conventional antihypertensive therapies in patients with the methylenetetrahydrofolate reductase (MTHFR) 677TT genotype but without apparent cardiovascular disease. Although this was a small trial with only 91 participants, they found that blood pressure control rates increased from 32% to 60% with the addition of riboflavin to treatment regimens in at risk patients with this genotype[5].

Welma Stonehouse et al designed a study to determine whether adding a docosahexaeonic (DHA) supplement would improve cognitive functioning in healthy adults. They also studied whether sex or the apolipoprotein E (APOE) genotype would affect the response to the DHA supplementation. This randomized control trial had a total of 176 participants ranging from 18 to 45 years old. Participants had to be nonsmokers and have a low dietary intake of DHA. They were randomly assigned to receive either the placebo or the DHA supplement. The trial concluded that DHA supplementation did improve memory and the reaction times of memory as well. In addition, sex affected the outcome. The researchers found that various memory functions were improved in the two different sexes. They suggest further studies must be completed in order to fully understand the effects[6].

The articles outlined above were reviewed in order to research the theory that nutraceuticals have a need for more evidence-based use. While not all of the articles had conclusive or even favorable outcomes, they do support the need for more research and therefore more educated usage of nutraceuticals. With more trials comes more knowledge, and with more knowledge comes more appropriate use. Another possible outcome that may arise with additional trials would be the ability to enforce more standardization laws on industries that manufacture such products.

Current Good Manufacturing Practices (cGMP) are regulations enforced by the FDA. The FDA ensures that drug manufacturing processes meet basic objectives under the cGMP. Under these practice designs, monitoring and control of manufacturing processes are observed and regulated. Facilities where production takes place along with materials and equipment are inspected to assure quality standards.

Unlike manufactured pharmaceutical drugs, nutraceuticals are not widely regulated by the FDA. In fact, the FDA is not required to demand registration or grant approval from dietary manufacturing companies prior to marketing a product[7]. This is due to the Dietary Supplement Health and Education Act (DSHEA) of 1994, which states it is the sole responsibility of the developers and manufacturers to ensure a safe and beneficial product before marketing. This limits the FDA from intervening during dietary product manufacturing and states that a manufacturing company is required to submit official documentation of ingredients used only when marketing a product with "new dietary ingredients"[8].

The FDA's responsibility is to oversee product-labeling, claims made by the manufacturer regarding the product, and package inserts. The Federal Trade Commission (FTC) on the other hand specifically regulates the advertisement of dietary supplements [8]. DSHEA regulates health claims of dietary supplements, but manufacturers and marketers are not required to prove the safety or efficacy of their products. While DSHEA strives to improve the safety and labeling of dietary supplements, dietary supplement manufacturers do not conduct clinical studies like pharmaceutical manufacturers do and thus are held to a different standards[9].

According to DSHEA, the dietary supplement can state that these products can offer nutritional support to individuals with nutrient-deficient diseases, but the companies are expected to write that the FDA has not evaluated their statements. Further, they must state that this product is not intended to diagnose, treat, cure, or prevent any disease. The FDA expects that nutraceuticals are manufactured under cGMPs and gradually the FDA is moving toward more rigorous regulations for nutraceuticals.

In the global consumer market nutraceuticals are an ever-growing industry and until recently, the manufacturing and quality control of these products have been largely unregulated. Requirements for expiration dating, supporting data and testing methods validity are unclear. These confusing regulatory requirements result in inconsistency and inefficient regulation therefore bringing forth the challenge of stability testing of nutraceuticals[10].

Using an evidence-based approach for nutraceuticals can provide healthcare providers and consumers with evidence regarding the selection and use of these products. Selection and use of nutraceuticals can be specific for each patient's given intervention and desired outcome to decrease healthcare costs and aid in disease prevention and treatment. There is a dire need for further research to aid healthcare providers and consumers in making more evidence-based decisions regarding nutraceutical use.

There is also a critical need for nutraceutical industries to embrace current good manufacturing practices to ensure that consumers have safe, efficacious products. Clinical studies giving rise to evidence based medicine would yield more accurate labeling and not only be beneficial for the industry to have statements of worth on the product but also solidify the trust of the consumers. Consumers can be assured the product

is following cGMPs and that reliable, scientific methods were used to support the products. The global market for nutraceuticals is ever growing and all nutraceutical manufacturers should comply with and embrace cGMP to ensure safe, quality products for consumers. The goal is to have all nutraceutical manufacturers worldwide follow cGMP in order to provide consumers with safe, effective and high quality products that are imperative in promoting a healthy lifestyle.

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