Perspective

Drug Testing and Analysis

Received: 27 April 2015 Revised: 16 July 2015 Accepted: 16 July 2015 Published online in Wiley Online Library: 2 November 2015

(www.drugtestinganalysis.com) DOI 10.1002/dta.1855

Dietary supplements: What's in a name? What's in the bottle?

Donald M. Marcus*

The Dietary Supplement Health and Education Act of 1994 (DSHEA), which arbitrarily classified herbals and other medicinal products as dietary supplements, obscured fundamental differences between two classes of products. Authentic supplements to the diet, such as multivitamins or calcium, have nutritional value and are safe. Herbals are used worldwide as medicines, they do not supplement the diet, they may cause severe adverse events, and they should be regulated as medicines. DSHEA also prevented the Food and Drug Administration (FDA) from effectively regulating herbal supplements as medicines. One consequence of weak FDA regulatory oversight is the poor quality of herbals. FDA inspections of manufacturing facilities have revealed violations of good manufacturing practices in over half of facilities inspected, including unsanitary conditions and lack of product specifications. Moreover, many "all natural" herbals marketed for weight loss, enhancement of sexual health and improving sports performance are adulterated with prescription and over-the-counter medications that have caused adverse cardiovascular events. New procedures to authenticate the identity of plants used in herbals will neither detect adulteration by medications nor provide assurance of appropriate pharmacological activity or safety. Nonvitamin, nonmineral "supplements" should be regulated as medicines, but revision or repeal of DSHEA faces strong opposition in Congress. The marketing of botanical supplements is based on unfounded claims that they are safe and effective. Health professionals need to inform patients and the public that there is no reason to take herbal medicines whose composition and benefits are unknown, and whose risks are evident.

Keywords: dietary supplements; botanicals; herbals; regulation; quality control

Nomenclature

Articles on dietary supplements frequently begin with: 'Over 60% of Americans take dietary supplements.' But what are they actually putting into their bodies, a multivitamin or a misnamed medicine? Prior to the Dietary Supplement Health and Education Act of 1994 (DSHEA),[1] the category of dietary supplements included only multivitamins and minerals. By arbitrarily classifying herbals and other medicinal products as dietary supplements, DSHEA obscured fundamental differences between two classes of products. There is no scientific basis for calling herbals 'supplements'. Authentic supplements, such as multivitamins or calcium, have nutritional value and are safe when used in recommended doses. Botanicals are used worldwide as medicines. They do not supplement the diet, and they may cause severe adverse effects. As noted by the late Dr Varro Tyler, an authority on the medicinal use of plant products, herbals are 'crude drugs of vegetable origin utilized for treatment of disease states'.[2]

Because consumers believe that all dietary supplements are harmless, the new nomenclature greatly increased sales of herbals and other supplements, especially for weight loss, boosting energy, and promoting sexual vigor. Moreover, the legislation, which was essentially written by the supplement industry, prevents effective regulation of herbals and other medicinal supplements by the US Food and Drug Administration (FDA).

Quality control

In 2008, the FDA started inspections of facilities that manufacture dietary supplements. From 2008 to 2012, the agency found violations of good manufacturing procedures in half of the 450 firms inspected, and in two-thirds of 204 inspections performed in the first half of 2012.[3] The violations included lack of recipes for the products and unsanitary conditions, such as infestation by rodents. In 2014, the FDA inspected 255 dietary supplement manufacturing facilities in the United States and 228 in other countries.[4] Common infractions included not conducting a test to verify the identity of a dietary ingredient and/or 'not establishing product specifications for the identity, purity, strength, and/or composition of the finished dietary supplement'. An average of six infractions were noted at facilities that received a notice of noncompliance.

In a study of commercial herbal products, DNA was recovered from 91% of 44 samples made by 12 companies.[5] DNA barcoding analyses revealed that only 2/12 companies provided products that contained DNA of the plants listed on the label, and product substitution was noted in 30/44 samples. Fifty-nine percent of herbals contained plant species not listed on the labels, and 33% contained DNA that matched rice, soybeans, and wheat, potential allergens which were not listed on the label. Some of the unlisted herbals, including senna and feverfew, are potentially toxic.

The New York State Attorney General commissioned DNA barcoding testing of 78 bottles of commercial herbal supplements sold by Walgreens, Walmart, Target, and GNC.[6] No DNA from the herb listed on the label was found in 4/5 bottles. In addition, the bottles often contained fillers, including rice, asparagus, and houseplants. A bottle of ginkgo biloba that was claimed to be wheat-free and gluten-free contained wheat, houseplants, and powdered

* *Correspondence to: Donald M. Marcus, Department of Medicine, MS 285 Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA.*
E-mail: dmarcus@bcm.edu

Baylor College of Medicine, Houston, TX, 77030, USA

radish. Concerns have been raised that the absence of DNA may be an artifact caused by its destruction during the manufacturing process. In response to these findings, GNC announced the institution of new procedures to authenticate the plants used in its supplements, and to test for common allergens.[7]

Adulteration

Many 'all-natural' herbal supplements are adulterated by prescription and over-the-counter medications.[8,9] Weight loss products frequently contain sibutramine, which the FDA withdrew from the market because of its association with strokes and cardiovascular events. Many supplements for the enhancement of athletic performance contain analogues of amphetamines, and supplements for sexual health frequently contain sildenafil or other phosphodiesterase-5 (PDE-5) inhibitors.[10] To escape detection by regulatory agencies, many PDE-5 analogues have been synthesized. Seventy-five percent of sexual enhancement supplements seized in the Netherlands contained PDE-5 analogues.[11] There are eleven different families of phosphodiesterases that are active in a variety of metabolic processes. The FDA-approved PDE-5 medications inhibit only one family, but less specific analogues may inhibit receptors found in many organs, and their safety has not been studied.[10]

In a letter addressed to supplement manufacturers, FDA Commissioner Hamburg noted that the agency had 'issued warnings about 300 tainted products that can cause serious adverse events, including stroke, organ failure and death'.[12] Some adulterated products remain in the marketplace even after recalls.[13] Twenty-seven supplements recalled because of adulteration were tested at least six months after being recalled. Sixty-three percent (17/27) contained the same pharmaceutical adulterant identified previously by the FDA, and six contained one or more additional banned ingredients. Adulterated herbal supplements remain in the marketplace because the FDA's authority to mandate removal of supplements from the market is limited by DSHEA, and the fines for violations are small compared to the profits.

Because of concerns about purity and safety, some authors and health leaders recommend buying only supplements that have been approved by the US Pharmacopeial Convention (USP). The USP is an independent, non-profit organization that provides analyses of food ingredients, medicines, and dietary supplements to improve the quality and safety of those products. The USP claims that analyses in its new Herbal Compendium 'establish standards for the identity, strength, quality and purity" of herbal products'.[14] USP tests provide useful information about contamination by microbial products, metals, and pesticides, and confirm the identity of the plant. However, analyses for the presence of all undeclared pharmaceutical compounds are not performed because of the enormous number of pharmaceuticals and novel analogues. Moreover, the meaning of USP's claim about verifying 'strength' of the herbals is unclear. Strength implies pharmacological activity, but the monographs provide no data about activity, which would be difficult to do because the active ingredients of most herbals have not been identified. The use of marker compounds for standardization does not provide assurance of pharmacological activity. *Unqualified* claims that USP analyses provide assurance of purity, quality, and strength are not justified by the data provided. In summary, new procedures to improve the quality of herbals will not guarantee either purity or standardized pharmacological activity.

Safety

A major factor in the promotion of herbals is the claim that they are gentle and safe because they are natural, in contrast to foreign, powerful, and toxic purified medications. In reality, the active ingredients of herbals are chemicals that act on the body in the same manner as purified medications, and have similar potential for benefit or harm. For example, *Aristolochia* sp. plants have been used worldwide in botanicals for over 1000 years. They were recently found to cause outbreaks of aristolochic acid nephropathy: interstitial nephritis, renal failure, and carcinomas of the upper urinary tract.[15] Naturally occurring aristolochic acids are among the most potent human carcinogens known.

Until recently, manufacturers were not required to report adverse events caused by supplements to the FDA, so most of our knowledge of supplement toxicity has come from Poison Control Centres and Emergency Rooms.[16] The FDA has estimated that dietary supplements cause 50 000 adverse events annually.[17] The most common adverse events are hepatic and renal damage, similar to those caused by FDA-approved medications. A prospective study of drug-induced liver disease found that approximately 20% of cases of acute liver failure in the United States were associated with the consumption of dietary supplements.[18] The FDA issues class I recalls of drug products for which there is a reasonable probability that use or exposure will cause serious adverse consequences or death. Moreover, from January 2004 through December 2012, 51% of recalled products were dietary supplements that were adulterated by unapproved drugs.[19]

Efficacy

Claims for the efficacy of plant extracts are based on their long history of use, and on older clinical trials funded by manufacturers. Systematic reviews and meta-analyses of those trials concluded that they were uninterpretable because of defects in design and interpretation, and publication bias.[20] Rigorous clinical trials supported by the National Institute of Health have found no benefit beyond a placebo effect for a number of popular herbals and supplements, including Echinacea, ginkgo biloba, ginseng, black cohosh, isoflavones, saw palmetto, and glucosamine.[21] Although some medications currently in use were originally identified in plant extracts, the vast majority of herbals have not been evaluated in clinical trials. Their perceived efficacy is based on traditional teaching and on placebo effects.

Conclusions

A fundamental question has been overlooked in recent articles about the quality of plant extracts: Is there any reason to take herbals? Their marketing is based primarily on the unfounded claims that they are safe and effective. Their only potential advantages – lower costs and the convenience of avoiding medical appointments – are outweighed by their hazards and uncertain efficacy.

Herbals and other medicinal products that were designated as supplements by DSHEA should be regulated as medicines. That would require revision or repeal of DSHEA, which is arguably the worst health care legislative act of the twentieth century.[22] Although efforts to amend DSHEA have been blocked by influential congressmen who supported its passage, they should be continued. However, the immediate need is to provide better information to the public. Most supplements are self-prescribed, and people use them based on misleading information on the Internet and in the media. Health professionals need to communicate more effectively to patients and to the public that there is no reason to consume products whose benefits are unknown and whose risks are evident.

References

[1] Dietary Supplement Health and Education Act (DSHEA, Public Law 103-417, 25 October **1994**; Codified at 42 USC 287C-11.
[2] J. E. Robbers, V. E. Tyler. *Tyler's Herbs of Choice. – The Therapeutic Use of Phytomedicinals*, The Hawthorne Press, Inc., New York, **1999**, pp. 1.
[3] T. Tsouderos. Dietary supplements: Manufacturing problems widespread, FDA inspections show. Available at: http://articles.chicagotribune.com/2012-06-30/news/ct-met-supplement-inspections-20120630_1_dietary-supplements-inspections-american-herbal-products-association [21 April 2015].
[4] ConsumerLab.com. FDA finds problems at 62% of supplement manufacturing sites in US and abroad. Available at: https://www.consumerlab.com/recall_detail.asp?recallid=10799 [21 April **2015**].
[5] S. G. Newmaster, M. Grguric, D. Shanmughanandhan, S. Ramalingham, S. Ragupathy. DNA barcoding detects contamination and substitution in Norh American herbal products. *BMC Med.* **2013**, *11*, 222.
[6] A. O Connor. New York Attorney General Targets Supplements at Retailers. Available at: http://well.blogs.nytimes.com/2015/02/03/new-york-attorney-general-targets-supplements-at-major-retailers/ [27 April 2015].
[7] A. O Connor. GNC to strenghten supplement quality controls. New York Times Available at: http://well.blogs.nytimes.com/2015/03/30/gnc-to-strengthen-supplement-quality-control/ [27 April 27 2015].
[8] FDA. Tainted products marketed as dietary supplements potentially dangerous. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm236967.htm [22 April 22 2015].
[9] P. A. Cohen. American roulette – Contaminated dietary supplements. *N. Engl. J. Med.* **2009**, *361*, 1523.
[10] P. A. Cohen, B. J. Venhuis. Adulterated sexual enhancement supplements. *More than mojo. JAMA Intern Med*. **2013**, *173*, 1169.
[11] B. J. Venhuis, D. de Kaste. Towards a decade of detecting new analogues of sildenafil, tadalafil and vardenafil in food supplements. *J. Pharm. Biomed. Anal.* **2012**, *69*, 196.
[12] M. A. Hamburg. Letter to manufacturers of dietary supplements. Available at: http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/MedicationHealthFraud/UCM236985.pdf [21 April **2015**].
[13] P. A. Cohen, G. Maller, R. DeSouza, J. Neal-Kaback. Presence of banned drugs in dietary supplements following FDA recalls. *JAMA*. **2014**, *312*, 1691.
[14] USP. New compendium offers freely available testing standards to help ensure the quality of herbal ingredients used in traditional medicines. Available at: http://www.usp.org/sites/default/files/usp_pdf/EN/aboutUSP/pressRoom/ga055nl_summer13_standard_2013-06.texterity.pdf [21 April 21 2015].
[15] A. P. Grollman. Aristolochic acid nephropathy: Harbinger of a global iatrogenic disease. *Environ. Mol. Mutagen*. **2013**, *54*, 1.
[16] P. A. Cohen. Hazards of hindsight – Monitoring the safety of nutritional supplements. *N. Engl. J. Med.* **2014**, *370*, 1277.
[17] Dietary Supplements. FDA Should Take Further Actions to Improve Oversight and Consumer Understanding. United States Government Accountability Office. GAO-09-250, January **2009**.
[18] V. J. Navarro, H. Barnhart, H. L. Bonkovsky, T. Davern, R. J. Fontana, L. Grant, K. R. Reddy, L. B. Seeff, J. Serrano, A. H. Sherker, A. Stolz, J. Talwalkar, M. Vega, R. Vuppalanchi. Liver injury from herbals and dietary supplements in the U.S. Drug-induced Liver Injury Network. *Hepatology*. **2014**, *60*, 1399.
[19] Z. Harel, S. Harel, R. Wald, M. Mandani M, C.M. Bell. The frequency and characteristics of dietary supplement recalls in the United States. *JAMA Intern. Med.* **2013**, *173*, 926.
[20] R.B. Bausell. *Snake Oil Science. The Truth About Complementary and Alternative Medicine*. Oxford University Press. New York. Chapters 11 and 12 **2007**.
[21] P. Offit. Studying complementary and alternative therapies. *JAMA*. **2012**, *307*, 1803.
[22] D. M. Marcus, A. P. Grollman. The consequences of ineffective regulation of dietary supplements. *Arch. Intern. Med.* **2012**, *172*, 1035.