Narrative Review: The FDA's Perfunctory Approach of Dietary Supplement Regulations Giving Rise to Copious Reports of Adverse Events

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Abstract

***Background**: The Food and Drug Administration (FDA) originated from the passage of the 1906 Pure Food and Drugs act aimed to rein in the long-standing abuse in the consumer product marketplace. The act was passed to prohibit interstate commerce of misbranded and adulterated foods, drinks, drugs. Thus, promoting the FDA's mission to protect the public health by regulating human and veterinary drugs, biological products, medical devices, food supply, cosmetics, and tobacco to ensure safety, efficacy, and security. Progressing further in 1994, the Dietary Supplement Health and Education Act (DSHEA) was established designating specific label requirements, providing regulatory framework, and authorizing the FDA to promulgate good manufacturing practices for dietary supplements. This act defined and classified "dietary supplements" and "dietary ingredients" as food requiring all over the counter products (OTC) products to consist of labeling that is easy to understand and meets the FDA quality, effectiveness, and safety standards. However, under the umbrella of OTC products, the FDA fell short in its regulation of the expansive dietary supplement market. The objective of this study is to discern how the lack of efficacy in the FDA's regulations of OTC dietary supplements inevitably inspired more harm than benefit.*

***Methods**: This review comprised of case studies including young adolescents and adult consumers who experienced adverse events from the use of dietary supplements. Products which showed highest prevalence in adverse event reports through the Food and Drug Administration CFSAN Adverse Event Reporting System (CAERS) included but not limited to; Vitamin E (vitamin derivative), Beta-sitosterol (plant sterol) Yohimbine, Kava Kava Kratom, Garcinia Cambogia, (herbal products) and OxyElite Pro (marketed weight loss product). The primary endpoint was evaluating the FDA's regulations on dietary supplement safety protocols. The secondary endpoint was assessing the actions of the FDA in response to these case events.*

***Results**: Overall, between 2004 to 2021, a total of 79,071 adverse events related to the use of dietary supplements were reported to the Center for Food Safety and Applied Nutrition. Vitamin E products for example, marketed for decades for their antioxidant benefits in turn have shown significant evidence of toxicity and an increased risk of bleeding outweighing its potential benefit. The FDA's response was simply implementing a label guideline update, yet this update had evidence of minimal effect as the number of cases gradually continued to increase. Likewise, herbal products such as Kava Kava, Yohimbine, Kratom, and Garcinia Cambogia, in addition to weight regulating products, such as OxyElite Pro and HydroxyCut, have been linked to organ failure, hepatic, renal, cardiac toxicity, and death respectively. The FDA merely responded through instating public consumer warnings of their effects with consumption and limited recalls of certain products.*

***Conclusion**: With the easy accessibility of these products, the general public is more inclined to its use without proper guidance and monitoring from their healthcare team, posing as a major concern for possible interactions, contraindications and unfavorable outcomes. With proper implementation of stringent regulations post findings from increased studies on efficacy and safety, cases of adverse events could have been reduced significantly or averted completely. The FDA's minimalistic efforts consisting of only post-marketing monitoring and retrospective actions of label modifying have time and time again shown flaws as seen in the growing series of reports. By emending the over-the-counter supplement review process to reflect that of prescription medication, the magnitude of adverse events can be diminished. The process should include preclinical research in addition to clinical research, FDA thorough examination of data prior approval and post marketing surveillance.*

Keywords: Nutraceutical regulation, Dietary supplements at FDA, Supplements adverse events

Introduction

The Food and Drug Administration (FDA) is responsible for regulating human drugs and biological products, animal drugs, tobacco products, food, medical products, electronics that emit radiation and cosmetics with a mission to protect the public health.[1] Under the umbrella of products that are regulated, a large subset comprises of dietary supplements. The multibillion-dollar dietary supplement industry dating back to the mid-20th century was not officially regulated by the FDA until 1994 DSHEA act yet still the FDA's role was more so reactive than proactive, posing as a major threat to the public health.[1] Under the DSHEA act, the FDA has the authority to regulate both finished dietary supplement products and dietary ingredients prohibiting and acting against manufacturers and distributers from marking adulterated or misbranded products.[1] However, due to supplements being regulated under a different set of regulations not covering "conventional" foods and drug products, the FDA is not authorized to review dietary supplement products for their safety and efficacy prior to marketing.[1] Millions of people in the United States consume these dietary supplements in efforts to maintain or improve

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DOI: https://doi.org/10.24926/iip.v14i1.4989

health, however given this limitation in systematic monitoring, the public is placed at a higher risk than benefit.[2] With the lack of governmental oversight, several dietary supplements containing harmful ingredients are not investigated until significant adverse cases are reported of which the delay in action leads to compromised health.

Methods

This review focused on dietary supplement reported adverse events between 2004 to 2021 from the Center for Food Safety and Applied Nutrition. Data collection was retrieved from various databases (e.g., Embase, NIH, and Pubmed) and hand searching through CAERS database consisted but not limited to adverse events involving the use of Vitamin E (vitamin derivative), Beta-sitosterol (plant sterol) Yohimbine, Kava Kava Kratom, Garcinia Cambogia, (herbal products) and OxyElite Pro (marketed weight loss product).

Results

Vitamin E is a fat-soluble vitamin marketed to potentially delay coronary heart disease, protect against cancer by enhancing immune function, reduce oxidative stress contributory to age-related macular degeneration (AMD) and provide protection against cognitive decline through its antioxidant properties.[3] Aside from supplementation, vitamin E can be derived from diet consisting of meat, avocados, fortified cereal, leafy greens, and oils (canola, olive, vegetable).[3] Vitamin E in the dietary supplement market can be found in two forms: the natural form (RRR-alpha-tocopherol) and the synthetic form (all-rac-alpha-tocopherol).[3] As per the FDA daily intake requirements, Vitamin E consists of 15mg of alpha-tocopherol from previous recommendations of 30 IU. However, evidence of potential harm with supplementation exists and must be considered and balanced with potential therapeutic benefits. For one, vitamin E supplementation has documented interaction with several routine medications including alkylating agents, antitumor antibiotics, anticoagulants, antiplatelets, CYP450 substrates, statins, niacin, and vitamin K. In 2005, a 50-year-old woman reported excessive postoperative bleeding with the causative agent identified as vitamin E (400 IU) prior to surgery. Vitamin E was discerned as the culprit for the substantial bleed due to its ability in lowering platelet adhesion via protein kinase C inhibition.[4] Likewise, significant major adverse events including increased risk of prostate cancer and increased recurrence of head and neck cancer with the consumption of vitamin E (400IU) was reported in large population studies. [5,6] Although FDA established the recommended daily intake for adults, the general dietary supplement label of vitamin E does not include any potential risk or an upper intake limit.[7] Though the FDA has updated labeling requirements to exclude terminology consisting of “indications”, “precautions” and “contraindications”, the generalized form can be contributory to harm due to the proposed lack of emphasis on synergistic effects. For example, the vitamin E label states “if you are pregnant, nursing, taking medication, have vascular disease or blood clotting issues, consult your physician before use” despite the label warning consumers on conceivable interactions or contraindications with intake, it does not account for the severity in potentiated harm with the use of concomitant medications and over the counter products.

Beta-sitosterol is an organic compound found in plants alone or in combination with other plant sterols to reduce levels of blood cholesterol by blocking cholesterol absorption as well as improve urinary flow and symptoms of benign prostatic hyperplasia.[8,9] Beta-sitosterol is promoted to be safe when consumed at a maximum of 20 grams daily with potential mild side effects being nausea, indigestion, diarrhea, and constipation.[8,9] Although marketed to be a harmless product, over a thousand adverse events regarding the use of a prostate support supplement called Super Beta Prostate was reported to the The Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS) in the past two decades.[10] Majority of the reports stated that hematuria was present after the consumption of Super Beta Prostate. The official causation was never determined, nor any advisory reports were released by the FDA addressing this issue.[11] Regardless, Super Beta Prostate continues flourishing on the dietary supplement market today with over 15 million bottles sold.[11]

Yohimbine, an indole alkaloid compound derived from the bark of the Pausinstalia yohimbe evergreen tree in central and western Africa; marketed and approved as both a prescription and dietary supplement for its aphrodisiac properties and enhancement in sexual performance by increasing blood flow and nerve impulses.[12] Currently Yohimbine efficacy as a dietary supplement remains ambiguous with limited studies showing evidence in its effectiveness for erectile dysfunction, angina, athletic performance, and weight loss. In a recent report released by the California Poison Control System, 238 over the counter Yohimbine-related adverse drug events (ADE) were documented from 2000 to 2006, of which 134 cases were escalated to hospitalization. Common documented adverse events included GI distress, tachycardia, anxiety, hypertension, flushing/erythema, diaphoresis, tremor, and chest pain.[13] Severe ADE’s constituted myocardial infarctions, atrial fibrillation, QTc prolongation, seizures, acute renal failure, and priapism.[13] In 2007, AAPCC’s National Poison Data System disclosed that 60 Yohimbine exposures out of the 277 reported had mounted to causing moderate to severe harm.[14] Nevertheless, despite the dubious safety profile of Yohimbine supplements and significant reports of adverse events, the FDA has yet to fortify their regulation on OTC Yohimbine products. Under the jurisdiction of the natural dietary supplement sector, in 2003 the FDA had only issued a warning to consumers regarding adulterated Yohimbine products such as Stamina RX and Uropin which were detected to be contaminated with tadalafil.[15] Similar to other dietary supplements, Yohimbine’s side effects were failed to be mentioned and reinforced in its product labeling. On the other hand, the prescription form of Yohimbine with the addition of hydrochloride, is FDA regulated. However, after a safety analysis, this compound has also been

DOI: https://doi.org/10.24926/iip.v14i1.4989

found to be notoriously linked to an increased prevalence in cardiovascular events including but not limited to myocardial infarctions, seizures, and acute neurotoxicity.[13]

Kava Kava also known as kava pepper, kava root, kawa and Piper methysticum, a dietary supplement and member of the pepper family native to the Pacific Islands and used commonly for its anxiolytic properties and insomnia benefits.[16] Kava Kava exhibits its benefits through the use of kavapyrones which act through a similar mechanism as alcohol and promote relaxation benefits.[16] Research has shown however, that the use of Kava Kava is interlinked with significant fatal liver injury and damage.[17,18] Kava Kava has also notably been documented to cause digestive upset, headache, dizziness, and long-term doses have been seen to cause kava dermopathy in which dry, scaly flaky skin with yellowing skin discoloration has been noted. [16,17] Cases of potential hepatotoxicity with the use of this agent have been reported in multiple nations causing France, Switzerland, Canada, Germany, and Australia to issue a countrywide ban. In Europe a total of 36 cases of kava-linked hepatitis were reported between 1990 to 2002.[18] Despite many adverse event reports, the FDA only issued a Consumer Advisory without initiating further stringent control.[17,19] As of now Kava supplements still remain as the cornerstone anxiety alleviating supplements for consumers in the United States. In 2007, the FDA had issued new manufacturing standards to address design and construction of the manufacturing plants. However, this does not resolve the major concern of the adverse effects precipitated from the use of the Kava kava plant.[17,19]

Kratom, yet an herbal supplement, extracted from the Mitragyna speciosa tree indigenous to Southeast Asia is commonly utilized for its stimulant-like effects in increasing energy and alertness as well as analgesic properties through pain relief and relaxation. Kratom is typically consumed by swallowing raw plant matter in the form of capsules or powder mixed into food and drinks, brewing the leaves as a tea, or taken as a liquid extract. In 2020, the National Survey on Drug Use and Health reported an estimated 0.8% (2,101,000) individuals 12 years of age and older who engaged in the use of Kratom.[20,21,22] Although Kratom users reckon its benefits supersede potential harm, research has deduced the side effects and safety issues outweigh any of the said potential benefits.[22] Kratom's known side effect profile consists of weight loss, dry mouth, liver damage, chills, change in urine, constipation, nausea, and vomiting.[22] However, the CAERS received 595 reports from 2004 to 2021 in addition to about 1800 reports from 2011 to 2017 to the poison control centers in the United States regarding spontaneous seizures, spikes in high blood pressure, and death in individuals documented to have exploited this supplement.[10,22] The United States and international agencies have expressed concern that Kratom may cause serious harm and restrictions on sales have been implemented in several countries excluding the U.S.[20] In 2021, the World Health Organization (WHO) expert committee on drug dependence examined the evidence on Kratom's health effects and concluded that there is insufficient evidence of adverse effects that would warrant additional critical review or inclusion in the United Nations list of internationally controlled substances.[20] In minimal efforts to reduce the impact of Kratom, U.S Marshals at the FDA's request, seized 25,000 pounds of raw Kratom in 2014 and 90,000 bottles of dietary supplement labeled as containing Kratom in 2016.[23] However, as of date, the FDA has simply issued a warning to consumers not to use the Kratom products due to potential adverse effects yet, several products are currently still legal and readily available online and in many areas within the United States.[20,23]

Similarly, another dietary supplement Garcinia Cambogia, a native plant in India and southeast Asia well known for its joint pain and digestive symptom relief properties lacks adequate benefits in its safety and efficacy profile. In addition, the fruit rind containing hydroxycitric acid, was marketed for weight loss through inhibition of ATP citric lyase .[24] However, the efficacy of Garcinia Cambogia in weight loss remains inconclusive, whereas adverse events related to its use have been significantly increasing.[25] According to The CFSAN Adverse Event Reporting System (CAERS), over a thousand Garcinia Cambogia related adverse events were documented from 2004 to 2021, with symptoms ranging from headache, nausea, and vomiting to liver injury/failure and renal disorders.[10] In 2009, the FDA issued a warning to recall a common dietary weight loss supplement, HydroxyCut, due to 23 cases of reported drug induced hepatoxicity. One of the active ingredients in this supplement included hydroxycitric acid.[26] Although the recall did not specify the offending ingredient, it did give rise to additional studies which evaluated the use of Garcinia Cambogia and resulted with findings in the prevalence of liver damage.[10,27] A case report of a 52-year-old female with a no significant past medical history, was admitted for liver injury after documented intake of Garcinia Cambogia supplement and unfortunately during admission was escalated to requiring an emergency liver transplant.[28] Similarly, 22 cases of liver injury due to consumption of Garcinia Cambogia either alone or with green tea extract were identified in the Drug-Induced Liver Injury Network (DILIN) from 2004 to 2018.[29] Unlike the ban of Ephedra products due to evidence of inducing several toxicities, the FDA did not issue any restriction on Garcinia Cambogia containing supplements despite the reports and cases linked to its consumptions.

In addition in 2013, when the fat burner product OxyElite Pro Super Thermogenic was introduced to the dietary supplement industry and was marketed for weight loss and body building.[30] OxyElite Pro initially used dimethylamylamine (DMAA) in its product which was tested to increase weight loss, but FDA later banned the use of DMAA in nutritional supplements due to the increase in blood pressure and heart rate in animal studies. OxyElite Pro changed their formula by replacing DMAA with aegeline, a component found in the fruit from the bael tree.[30] Natural bael tree fruits and leaves have been used in ayurvedic

DOI: https://doi.org/10.24926/iip.v14i1.4989

medicine in Southeast Asia for the "treatment of digestive complaints and diarrhea". However, the aegeline purity in Oxyelite Pro was not clear and was found to be a synthetic product made in China.[30] Upon finding the ingredient "lacking history of use or other evidence of safety" the FDA issued a warning letter to USPlabs in October 2013 and advised consumers not to use any dietary supplement labeled OxyElite Pro or VERSA-1 and to contact their physician if they believe they have been harmed by using the product.[31,32] Nevertheless, having been on the market for a few months and consumed by several, irreversible damages were seen in at least 50 consumers who experienced incidents of acute liver injury with an overall mortality rate of 10% associated with OxyElite Pro usage.[30,31] In efforts to reduce the impact of this product, Dr. Linda Wong and her colleagues at the University of Hawaii had reported their findings through MedWatch however, unfortunately no actions were taken until much later.[3]

Discussion

It is long overdue that this gap in protecting public health requires action from the FDA; in spite of the fact that, the FDA has issued countless warnings about the use of supplements sold for preconceived notions of potential benefits in weight loss, muscle building, sexual function, energy or sport performance, these products still remain widely marketed and used nationwide with no stringent control. In a study published in 2019 in the Journal of Adolescent Health, researchers analyzed adverse reports including death, disability and hospitalization in individuals aged 0 and 25 years of age between 2004 and 2015 within the U.S. Food and Drug Administration Adverse Event Reporting System database.[34] The study reported 977 single supplement related adverse events within the target age range of which 40% involved serious medical outcomes (death and hospitalization).[34] Supplements which were sold with the promise of promoting weight loss, muscle building and energy were associated with almost an increase in three times the risk of a severe medical outcome compared to vitamins.[34] Whereas supplements promoting sexual function enhancement and colon cleansing were associated with two times increase in risk compared to vitamins.[34] Nevertheless, benefits outweighing the risk with the use of vitamins remain ambiguous.

Conclusion

Given the easy access to dietary supplements encompassing vitamins, the public is more prone to resort to its consumption as opposed to contacting their physician for a regulated prescription medication, advice, or device. Having only touched the surface of regulation, the FDA is in dire need of reform to control dietary supplements and prevent adverse effects through advancements in studies of efficacy and safety in addition to labeling updates emphasizing the potential harm stemming from use of these products. It is therefore highly recommended that this public health gap be closed by the FDA requiring safety and efficacy proof prior to marketing for supplements, as is done with most other health related products. By implementing the same rigorous procedure of prescription medication review prior to marketing including preclinical research followed by clinical research and thorough FDA examination preceding approval and post marketing monitoring, the significance in adverse events can be vastly reduced.

The opinions expressed in this paper are those of the authors.

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