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Investigation of Adverse Reactions Reported with Dietary Supplements in United States Global Safety Database

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Abstract: The aim of the study is to analyze the adverse reactions reported with consumption of dietary supplements in United States safety database (CAERS) to understand their frequency and severity. Data from CAERS database was analyzed for the period between January 2004 and March 2020. The data retrieved from CAERS was presented for trend of adverse events reported with food and dietary supplements marketed in US including seriousness, frequently reported dietary supplements in this database, type of adverse events and patient demographic information. The analysis of the database revealed a total of 69,266 cases reporting 103,503 different food products/dietary supplements and a total of 190,694 adverse events. Most frequently reported adverse events were related to Gastrointestinal disorders and most frequently reported product category was Vit/Min/Pro/Unconv diet. Almost 90% of the reported adverse events were serious in nature and frequently reported in female population. CAERS database provide important information regarding safety of nutraceuticals. Regulatory bodies in countries with large nutraceutical market should employ such measures to collect the safety data along with spreading awareness to increase the reporting of the adverse events related to nutraceuticals.

Key words - Adverse reactions, CAERS, Dietary supplements, Nutraceuticals, Nutrivigilance, Pharmacovigilance

I. INTRODUCTION

A pre conceived notion exist among the consumers that therapies that have natural origin are completely safe and does not carry any risk of adverse outcome. In addition, herbal remedies or nutraceuticals are being used from long time without significant toxicities. Some of these ingredients may be harmless but some are innate toxic e.g., chamomile has been documented in causing allergic reactions including asthma (1). Adverse reactions are not only associated with the herbal or nutraceutical ingredients but also attributed to (2-3):

- quality issues in herbal or nutraceutical preparations such as adulteration, contamination with harmful substances i.e., heavy metals, pathogenic micro-organisms, pesticides etc. Examples include:
  - marketing of fake plant products i.e., morphological substitutes. One such example of fake herbal species is adulteration with notoginseng in products claimed to contain Ginseng (4-6) Another such example includes adulteration of wild berries, black soyabean hull & rice extracts in preparations of bilberry fruits (*Vaccinium myrtillus L. Ericaceae*) (4,7)
  - contamination with heavy metal (mainly Cadmium (Cd), mercury (Hg), lead (Pb), and arsenic (As)) and pesticides (organophosphates, organochlorine, pyrethroid etc.) can lead to serious adverse outcomes including neoplasms, psychiatric disorders, neuro-degenerative disorders, respiratory disorders, cardiovascular toxicities, reproductive toxicities etc. (8-14)
- risks related to presence of potent pharmaceutical substances (such as corticosteroids and non-steroidal anti-inflammatory agents). Examples include:
  - some herbal preparations found to have small amount of steroids (e.g. betamethasone) which has led to corticosteroid related side effects (2).
  - Other examples include adulteration with antidepressants, laxatives, diuretics in weight-loss supplements, anabolic steroids in sports supplements and phosphodiesterase inhibitors in products claimed for sexual performance enhancement (15).
- medication errors such as unintended ingestion of incorrect medicinal plant species, incorrect dosing, errors in the use of herbal medicines both by health-care providers and consumers. Examples include:
  - misidentification of the medicinal plant species such as chamomile species of *Anthemis nobilis L.* and *Matricaria chamomilla L.* are easily confused with *Tanacetam* species due to similar appearances (4).
- adverse reactions arising from concomitant use with other medicines (i.e., drug-herb interaction). Examples include:
  - risk of life-threatening interstitial lung disease with concomitant use of some herbal medicines with interferons (2); reduction in pharmaceutical drug levels and other interactions with concomitant use of St John's wort (16-19); risk

of bleeding with simultaneous use of NSAIDs and Gingko biloba (20); many theoretical effects on warfarin are reported due to concomitant administration of herbal products; hence, not recommended for simultaneous administration with warfarin (21).

Considering the increased usage of herbal medicines and health supplements; monitoring & understanding of these adverse events are very important as it is being done for pharmaceutical drugs. As mentioned earlier, the adverse events may not be necessarily due to inherent nature of the nutraceutical ingredient but can be due to poor quality, adulteration or interaction; hence, it is imperative to distinguish the root cause of the adverse reactions so that a suitable mitigation measure can be adopted.

Safety surveillance of nutraceuticals i.e., detection, assessment, understanding and prevention of adverse events related to nutraceuticals is an efficient way to ensure safe use of these products. Hence, post marketing surveillance should be made mandatory by regulatory authorities of countries where nutraceuticals are marketed. Currently, very few countries have active surveillance systems to monitor and evaluate adverse reactions associated with nutraceuticals (2)

An adverse event after using medicinal product can be reported from multiple sources including spontaneous reporting directly by consumer or health care professional (HCP) (22-24), worldwide literature (25-27), clinical trial reports (interventional and non-interventional such as observational, studies) (28), Electronic health record (29-30) legal cases (31) and social media reports (32-33). These adverse events are processed in safety databases maintained by country regulatory authorities and/or the manufacturing companies. Some of the major countries/regions monitoring and databasing adverse events include United states of America (USA), European Union (EU) and Canada. The regulatory authorities in these countries/regions maintain publicly accessible databases (as per their access policy) as means of monitoring the adverse events of marketed drugs. These databases are Food & Drug Administration (FDA) Adverse Event Reporting System (FAERS), Eudravigilance medicines safety database and the Canada Vigilance Adverse Reaction (CVAR) (34-35). Additionally in USA, Center for Food Safety and Applied Nutrition (CFSAN) of FDA maintain a specific database named as CFSAN Adverse Event Reporting System (CAERS) which comprises of information pertaining to adverse event reports and product complaints that are submitted to FDA for foods, dietary supplements, and cosmetics. The current study is aimed to provide the analysis of the adverse reactions reported with consumption of different type of dietary supplements in CAERS database to understand their severity and frequency.

II. MATERIALS AND METHODS

Raw data (from January 2004 to March 2020) made publicly available by CFSAN is used for the current study which contained adverse events reported with food, dietary supplements and cosmetics (36). The events/cases reported solely for cosmetics were excluded from the analysis. The events in CAERS are coded to terms in terms of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs).

CAERS database is a tool for FDA to identify any signal or safety concern that might be associated with food or marketed supplement. It also assesses the manufacturer's compliance to regulatory requirements of marketing. The data in CAERS is raw data and does not confirm the association between the suspect product and the adverse event. This data is evaluated by specific clinical reviewers at CFSAN who evaluate the data and take appropriate action in case a potential safety concern (i.e., where a possible causal association between product and event) is identified. These actions may range from communicating the safety concern to consumers and HCPs to license cancellation and recall of the product from the market. The data in CAERS database is received either directly from consumers or HCPs or from the manufacturers as per regulatory obligations. Manufacturers are obliged to report any serious adverse event to FDA which is related to their dietary supplement. All these reports are databased in CAERS. The events are not limited to medical issues but also include product complaints such as packaging issues, product defects, off-taste or color etc.

The data from CAERS was analyzed to understand the trend of adverse events reported with food and dietary supplements from 2004 onwards in USA. Frequently reported dietary supplements and frequently reported adverse events were identified from the assessment of the database. Since, the seriousness of events and patient demographics plays a vital role in identification of any new signal of safety concern, the distribution of events based on their seriousness and age/gender distribution was also studied. For the age group distribution, categories specified in Table 1 were followed (37-38).

Table 1: Age Group Classification

Age group	Sub group	Age range
Pediatric	Neonates	from birth through the first 28 days of life
	Infants	29 days to less than 2 years
	Children	2 years to less than 12 years
	Adolescents	12 years to less than 22 years
Adults	Adults	22 years to less than 65 years
Geriatric	Elderly	65 years and over

Seriousness of the events was categorized based on the seriousness criteria defined by FDA (39). As per the criteria, the event is serious if the outcome is death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly or birth defect and important medical events (IME). IME include the events which can put the patient at risk and may require therapeutic intervention (medical or surgical). The examples of IME include emergency room treatment for allergic breathing difficulty (allergic bronchospasm), blood dyscrasias, convulsions where hospitalization is not involved. Patients developing addiction/ dependence or drug abuse are also considered as IMEs.

III. RESULTS

During the specified period of data availability (Jan-2004 to Mar-2020), a total 69,266 cases were reported for food and dietary supplements.

Of the total 69,266 cases, gender of consumers was not known in 47% of the cases. In the remaining reports, female consumers were almost double as compared to males (i.e., 34% as compared to 19%). The maximum exposure from these cases was noted for adults and elderly, which accounted for almost half of the cases (46.4%). The age distribution in these cases is shown in the Fig. 1.

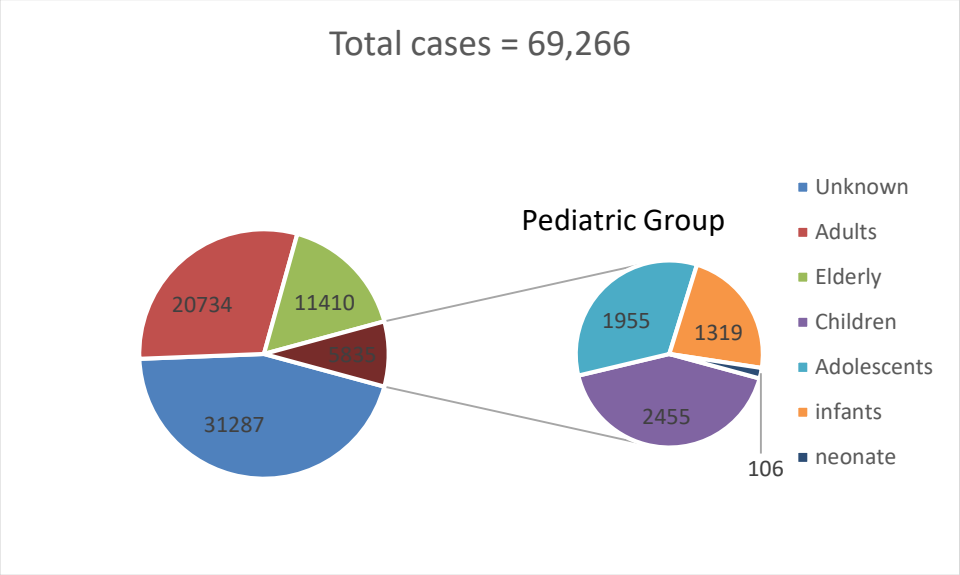

Figure 1: Age distribution among cases reported for food and dietary supplements in CAERS database

These 69,266 cases reported 103,503 suspect/concomitant food/dietary supplements. Of these 103,503 suspects/concomitants, information about the product was not available in 608 cases as they were falling under Exemption 4 criteria. Exemption 4 is a reference to the regulation (21 CFR 20.111 (c) (3)) that permits the FDA to withhold a product's name from the public (in order to protect trade secrets and commercial or financial information) when a report of harm has been submitted voluntarily by a manufacturer (40).

These 103,503 products were divided in to different food/supplement categories. Most commonly reported product category was vitamin/mineral/protein/ unconventional diet i.e., consumers using products in this category experienced highest number of adverse events (Table 2).

Table 2: Top 15 suspected/concomitant product categories with regards to adverse drug reactions in the CAERS database

S. No	Suspect/concomitant product category	Number (%age)
1	Vit/Min/Prot/Unconv Diet (Human/Animal)	67,631 (65.3)
2	Vegetables/Vegetable Products	3,583 (3.5)
3	Nuts/Edible Seed	3,551 (3.4)
4	Soft Drink/Water	2,908 (2.8)
5	Bakery Prod/Dough/Mix/Icing	2,905 (2.8)
6	Fruit/Fruit Prod	2,621 (2.5)
7	Fishery/Seafood Prod	2,603 (2.5)
8	Dietary Conventional Foods/Meal Replacements	1,767 (1.7)
9	Milk/Butter/Dried Milk Prod	1,679 (1.6)
10	Cereal Prep/Breakfast Food	1,549 (1.5)
11	Baby Food Products	1,337 (1.3)
12	Snack Food Item	1,213 (1.2)
13	Mult Food Dinner/Grav/Sauce/Special	1,187 (1.1)
14	Coffee/Tea	1,021 (1.0)
15	Ice Cream Prod	957 (0.9)
Total		103,503

A total of 190,694 adverse events were reported in 69,266 cases, which accounts for approximately 3 events per case. Of these 190,694 cases, approximately 90% of the events (n= 171,046) were serious. Most commonly reported events pertain to Gastrointestinal disorders (Table 3).

Table 3: Top 20 most frequently reported adverse drug reactions in the CAERS database

S. No	Adverse event (MedDRA PT)	Number (%age)
1	Diarrhea	12,562 (6.6)
2	Vomiting	10,554 (5.5)
3	Nausea	8,866 (4.6)
4	Abdominal pain	7,420 (3.9)
5	Malaise	5,129 (2.7)
6	Choking	4,534 (2.4)
7	Headache	3,897 (2.0)
8	Abdominal pain upper	3,485 (1.8)
9	Dyspnea	3,262 (1.7)
10	Hypersensitivity	3,115 (1.6)
11	Dizziness	3,080 (1.6)
12	Dysphagia	2,255 (1.2)
13	Pain	2,067 (1.1)
14	Fatigue	1,936 (1.0)

15	Pruritus	1,830 (1.0)
16	Burning sensation	1,701 (0.9)
17	Dysgeusia	1,625 (0.9)
18	Rash	1,587 (0.8)
19	Asthenia	1,559 (0.8)
20	Urticaria	1,512 (0.8)
Total		190,694

There was mixed trend from cases received every year. From 2004 to 2013, number of cases reported saw an increased trend every year, post which it decreased in 2014 followed by increase till 2016, when the number of cases peaked. After 2016, a decreasing trend was noted till 2019 (Fig. 2). Data of 2020 is not considered for this trend analysis as it was only available for 3 months i.e., till Mar 2020.

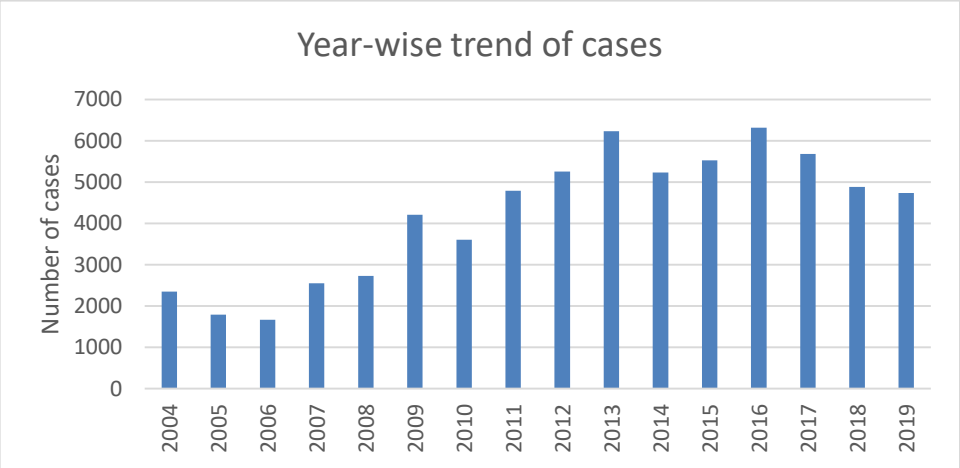

Figure 2: Trend of cases reported for food and dietary supplements in CAERS database from 2004 to 2019

IV. DISCUSSION

From the analysis of CAERS database, it was noted that majority of the cases in CAERS database were reported with unconventional food products, vitamins or minerals. Also, unlike widespread belief, we noted almost 3 events after use of every suspect/concomitant product and majority of these accounted for serious adverse events. Of these events, around 4,000 events reported an outcome of death/life-threatening condition. It was further noted that these adverse events frequently occurred in females as compared to male population. The results of this study were in line with the known published trends. A case series reported to the Italian health authority (National institute of Health) for herbal products used for weight loss, also noted that women were involved in 85% of the reports of suspected ADRs associated with herbal products (41) The study also detected that use of dietary supplements is associated with several ADRs including death and life-threatening outcome with causality reported as possible/probable/certain in majority of the cases. In Canada, Vohra et al. (42) presented the study of natural health products adverse reactions (SONAR). A probable causality of reported adverse events with the natural health product (NHP) use was revealed based on the analysis of the CAERS database. In the current study, the causal association of adverse events with suspect/concomitant products was not determined. However, considering the literature evidences, a causal role of these products in developing adverse events could not be denied.

Even though the awareness about risks associated with dietary supplements/nutraceuticals is increasing, the reporting of adverse events related to these products continue to be very low as compared to pharmaceutical products. This trend of low reporting is also consistent with a study performed by Sharma et al. (35) in which the review of FAERS and CVAR database revealed only 2.5% and 7% of cases reported with herbal products as compared to 97.5% and 93% cases with non-herbal products.

In conclusion, CAERS database provided valuable information focusing on adverse reactions with dietary supplements as suspect/concomitant products. Based on the results of the study, we consider that it is crucial to report and collect as many cases of adverse events with herbal products/nutraceuticals, as possible so that well studied scientific decision on adverse event association can be made. This will allow scientific committees to take suitable measures to identify any safety signal and to minimize the identified risks. Appropriate and robust surveillance systems should be developed by regulatory authorities especially in countries where consumption of these products is high. In addition, pertinent programs should be initiated to increase awareness regarding adverse event reporting channels among HCPs and consumers.

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