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# Dietary Supplements Containing Aegeline and DMAA (1,3-Dimethylamylamine) and their Role in Liver Injury

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**ABSTRACT**

*Aegeline is a constituent of the plant, Aegle marmelos, which has a long history of consumption as a food and traditional medicine. Due to the inclusion in a dietary supplement, OxyELITE Pro, which was apparently associated with liver injury in the fall of 2013 with a suspected cluster in Hawaii, has been the subject of speculation regarding hepatotoxic potential. However, in vitro, animal model and epidemiological data demonstrate a lack of hepatotoxic effects with aegeline. The ingredient, 1,3-dimethylamylamine (DMAA), was also formerly included in OxyELITE Pro and has also been the subject of speculation as to whether it is hepatotoxic. However, randomized controlled trials (RCTs), epidemiological and animal data do not support the notion that DMAA is hepatotoxic. Through an evaluation of the available data, a hypothesis is put forth which better explains the anomalous and contradictory nature of the "outbreak" which was thought to have occurred only in Hawaii and the few subsequent case reports in the mainland United States. Examples of other cases where exclusive reliance upon case reports and a temporal association have led to erroneous assumptions of causality are given. The data do not support a causal role of aegeline, DMAA or OxyELITE Pro in liver injury and instead indicate what may be one of the most prominent cases of a "pseudo-outbreak" and stimulated reporting. This is Part 1 of a 3 part article. Part 1 discusses aegeline and DMAA in detail along with the epidemiology of cases of liver injury purported to be linked with OxyELITE Pro.*

**Keywords:** OxyELITE Pro, Hawaii, Hepatotoxicity, Pseudo-outbreak, Stimulated reporting

## INTRODUCTION

OxyELITE Pro was a popular dietary supplement formulation which was apparently first marketed in late 2009 and contained the ingredient, 1,3-dimethylpentylamine, also known as 1,3-dimethylamylamine or most commonly known as DMAA, a sympathomimetic compound [1]. In April of 2012, the United States Food and Drug Administration (FDA) demanded that manufacturers selling DMAA cease doing so as it was the subject of a new dietary ingredient notification [2]. However, USPlabs disputed the FDA's conclusions and continued to include DMAA in OxyELITE Pro until April of 2013 when the company announced its intention to remove DMAA from their products; the DMAA-containing version of OxyELITE Pro, however, was apparently still available through July of 2013 while it was being phased out. In April of 2013, presumably in an anticipatory attempt to fill a void left by the impending removal of DMAA in products, an OxyELITE Pro formula was marketed which did not contain DMAA, but rather, an alkaloid called aegeline, which is found in parts of the *Aegele marmelos* plant (i.e., especially the leaves and fruit). Subsequently, two additional formulas with distinct ingredients (i.e., with the exception of containing aegeline, yohimbine, and caffeine) were also marketed [3]. The formula containing DMAA is referred to herein as OEP-OF (OxyELITE Pro-Old Formula), while that of the aegeline-containing versions are OEP-NF I-III (OxyELITE Pro-New Formula I-III).

In the fall of 2013, it was hypothesized that a dietary supplement, OxyELITE Pro, containing aegeline, was the cause of acute liver injury with a cluster in Hawaii and several subsequently reported cases in the United States mainland. Since that time, several groups of authors have put forth papers with specious arguments and conclusions. The data, for which those conclusions are drawn lack transparency, are contradictory and require clarification to explain the unresolved anomalies. The current hypothesis that OxyELITE Pro was hepatotoxic was based upon case studies, case series and descriptive epidemiology, none of which are able to demonstrate causality [4-13]. Furthermore, the published

cases actually implicate the wrong formulation of OxyELITE Pro (i.e., the DMAA-containing version, OEP-OF rather than the aegeline-containing versions, OEP-NF), while the potential presence of apparently counterfeit versions of OxyELITE Pro on the market may further confound matters [14]. A thorough and critical review of available published data provides strong evidence which causes the notion that aegeline, DMAA, and OEP-NF are hepatotoxic agents to become untenable. Additionally, this case perhaps demonstrates one of the most striking instances of a "pseudo-outbreak" and stimulated reporting to date. Several instances of cases where a temporal association alone led to an erroneous conclusion are also covered.

## METHODS

### Literature Search

As part of a general (non-systematic) review, PubMed and Google Scholar were searched for original research articles, reviews, reports, and letters to the editor which included an analysis of aegeline or 1,3-dimethylamylamine (DMAA) and hepatotoxicity or liver injury. Search terms included DMAA, 1,3-dimethylamylamine, dietary supplements, OxyELITE Pro, OEP, aegeline, hepatotoxicity, liver, liver injury. Publications retrieved were analyzed with respect to any association between aegeline, DMAA or OxyELITE Pro and hepatotoxicity. Statistical calculations were performed using Microsoft® Excel-add-in-DDXL (Redmond, WA, USA).

### An Introduction to Aegeline

**Use of *Aegle marmelos* as a food and traditional medicine without hepatotoxicity:** An overwhelming number of studies demonstrate the lack of any hepatotoxic effects from the *A. marmelos* plant, including extracts from the parts of the plant known to be rich in aegeline (e.g., leaves and fruit) (Tables 1 and 2). All parts of the plant are used as food (e.g., eaten directly or incorporated into drinks, candy, jams, preserves, and syrups) or medicine (e.g., widely used to treat type II diabetes in Ayurvedic medicine but is used for a wide variety of purposes) and have been consumed for thousands of years [15,16]. The plant leaf has also been studied in human trials and no liver-related side effects have been reported [17-20].

*A. marmelos* has never been associated with hepatitis or liver injury in the thousands of years it has been used in traditional Indian medicine. It has actually been used to treat jaundice and liver injury [35-40]. If the portion of the plant (i.e., the leaf) which contains the highest amount of aegeline (up to 4.13 mg/g according to a recent study by Avula, et al., which is in agreement with what others have reported) is used to treat jaundice and hepatitis, this is additional evidence refuting the notion that aegeline could cause hepatitis [41]. In various formulations, a total daily dose of 10 g or more of *A. marmelos* leaves is often used. Using the data from Avula, et al., for relatively fresh whole leaves, this would contain between 24 to 41 mg/day of aegeline [41]. Even using the lowest figure obtained Avula, et al., (1.26 mg/g), despite the fact that the sample wasn't fresh, this would yield approximately 12.6 mg/day of aegeline [41].

**Consumption levels of aegeline:** A study found that the average annual consumption of *A. marmelos* by certain indigenous tribes of India was 5 (±4.6) kg and was in the top 10 species collected and consumed by those tribes [42]. The young leaves and shoots of *A. marmelos* are eaten as a vegetable in Thailand and used as a seasoned food in Indonesia. The leaves are said to be consumed as a green salad in many Asian countries [16,43]. An infusion of the leaves is taken as a drink in the morning for a few weeks as a method of relieving peptic ulcer and is even given to infants to treat coughing and has been consumed daily by adults to improve memory. [44].

While a typical aegeline intake has not been formally calculated, a simple calculation derived from the results of Avula, et al., along with a typical or reference amount consumed per eating occasion, indicates that a 40 g serving of dried fruit could contain up to around 6 mg of aegeline, while a 140 g serving of fresh fruit could contain up to 22 mg of aegeline [41,45]. The leaves if consumed as a salad (i.e., 100 g serving) could contain between 126 and 413 mg of aegeline. Finally, candy and candied/pickled fruit could contain around 3 and 5 mg, respectively. If accurate, this level of consumption is within the range seen in the OxyELITE Pro and VERSA-1 products known to contain aegeline.

Finally, it should be noted that aegeline belongs to a class of molecules (i.e., hydroxyl cinnamic acid amides) which are commonly found in plants that are consumed by humans [46-50].

**Synthetic versus natural aegeline:** While it is clear that aegeline is commonly consumed in significant quantities in the diets of those in India and Southeast Asia, some have speculated that the synthetic (i.e., racemic) aegeline

found in the DMAA-free versions of OEP-NF (and in VERSA-1), could have been hepatotoxic, while the version found in the plant is not. First, it should be noted that prior to the study by Avula, et al., the aegeline found in the "bael" or *A. marmelos* plant was thought to be racemic [51-53]. However, even considering the more recent data it is clear that significant quantities of both the R and S enantiomers of aegeline are normally consumed with the S enantiomer predominating. For example, in some samples, around 33% consisted of the R-enantiomer. As an example from the Avula, et al., study, if 100 g of leaves are consumed, this would result in the potential consumption of anywhere between 126 to 413 mg of aegeline [41]. Of that, between 17 to 29% could be R-aegeline. Thus, between, approximately 21 mg to 37 mg of R-aegeline and 70 and 120 mg of R-aegeline could be consumed. These values are still within the range of the amounts that would be found in the OEP-NF (I-III) products. Furthermore, synthetic (racemic) aegeline has been studied in Wistar rats and failed to show any hepatotoxic effects, while demonstrating similar anti-oxidative, anti-inflammatory and hepatoprotective effects typically seen with *A. marmelos* extracts [54].

**Pharmacokinetic and *In Vitro/In Vivo* Studies on Aegeline:** In a study by Manda, et al., pharmacokinetic data on aegeline were gathered [55]. Mice were given a single 30 mg/kg dose of aegeline orally and this resulted in an elimination half-life of 1.25 hours, along with a peak plasma concentration and area under the curve (AUC) of 0.92 µg/mL (approximately 3.09 µmol) and 2 h*µg/mL, respectively. A calculated volume of distribution was 40 L, with distribution noted to the brain, kidney, and liver; extensive tissue distribution with relatively low plasma levels is rather typical for natural products. These data are useful when comparing the results of an *in vitro* cytotoxicity test in a human liver carcinoma cell line (HepG2) incubated with naturally occurring aegeline obtained from the leaves and fruit of the plant. The results showed 43.2% inhibition at the highest dose tested (i.e., 100 ug/mL or 336.3 µmol), still failing to reach an LC50 or IC50 at the highest concentration tested [56]. It is important to note that these are cancer cells. The reason for this testing was to evaluate compounds for their anti-cancer effects (i.e., the ability to inhibit the proliferation and cause the death of the cancer cells) [57]. Assuming that the kinetics of aegeline are linear, it would require more than 100 times a 30 mg/kg dose (i.e., 3,000 mg/kg) in mice to reach the highest concentrations evaluated, which still showed 42.3% inhibition, making such concentrations likely irrelevant to *in vivo* administration [55]. While selective accumulation in tissues such as the liver is possible, natural products have not generally shown the extreme level of selective accumulation (i.e., ~109-fold) necessary for this to be relevant. For example, various natural products have shown liver to plasma concentrations in the range of around 2:1 to 9:1 after oral administration [58-62]. Additionally, it is important to note that this ~109-fold difference is comparing cancerous human HepG2 cells *in vitro* with peak plasma concentrations achieved after an oral dose of 30 mg/kg in mice. It is unknown what the pharmacokinetic profile of aegeline would be in a human receiving 2 mg/kg (i.e., the total daily dose achieved with 3 capsules of OEP-NF), as compared to a mouse receiving 30 mg/kg. It seems unlikely that a 2 mg/kg dose of aegeline in humans would be equivalent to a 30 mg/kg dose in mice, making it even more difficult for the concentrations in the HepG2 cell line to be achieved in humans after oral administration. In any event, this 3,000 mg/kg dose is extremely high (more than 1,500 times greater) compared to the approximate 2 mg/kg total daily dose ingested with humans consuming OEP-NF. While the HepG2 cell line has been used to test for hepatotoxicity, it isn't considered as useful as other *in vitro* cell lines mainly due to the lack of metabolic activity. This lack of activity can also overestimate the toxicity of compounds that are extensively metabolized [63]. Whether or not cell death actually occurred is a vital piece of information and importantly, the authors of this study did not use a true cell death assay [56], but the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay which is an indirect way of measuring potential cell death by primarily assessing the dehydrogenase activity of the mitochondria and is only recommended as a preliminary means of assessing cell viability [64,65]. Galluzzi, et al., and others have elaborated on this and other pitfalls (e.g., medium overconsumption and excessive cell density can lead to underestimation of viable cells). The authors may have merely measured a moderate metabolic alteration rather than cell death. Epigallocatechin gallate (EGCG), on the other hand, demonstrated indications of toxicity at 100 µmol in HepG2 cells in an experiment that more directly assessed whether cell death occurred or not, as compared to the MTT assay [64,66].

In an attempt to determine if aegeline could potentially cause drug interactions resulting in hepatotoxicity, aegeline has also been examined for its effects upon cytochrome P450 isozymes, including CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2C19. The authors noted that it demonstrated only weak inhibitory activity for CYP3A4, with an IC50 value of approximately 76 µmol [52]. This is a concentration that wouldn't likely be reached without extremely high doses (i.e., close to 740 mg/kg) in mice [55].

Finally, in a recent study, synthetic (racemic) aegeline was administered (orally) at a dose of 20 mg/kg to aged albino Wistar rats fed a standard diet or a high cholesterol diet (HCD), for a period of 30 days. Those given aegeline along with a standard diet showed no evidence of hepatotoxicity as evidenced by a lack of change in liver histopathology and liver enzymes (alanine aminotransferase or ALT, aspartate aminotransferase or AST and alkaline phosphatase or ALP). In addition, synthetic aegeline, similar to *A. marmelos* extracts, clearly demonstrated hepatoprotective effects in response to the HCD via anti-oxidative, anti-inflammatory and lipid clearing effects. As the authors note, aegeline showed clear anti-steatotic effects. Interestingly, aegeline also reduced bodyweight gain in response to the HCD [54].

**An Evaluation of DMAA**

**A brief history:** DMAA (1,3-dimethylamylamine), a compound once used as a nasal decongestant by the trade name Forthane, has been included recently as an ingredient in a large number of dietary supplements (DS) for weight reduction and became the subject of speculation as to its potential as a hepatotoxic constituent of some DS products including OEP [2,67-69]. However, prior to such speculation, this compound had been on the market since 2006 and was not implicated by any published cases of liver injury or any regulatory announcements regarding liver injury [2,70,71].

First marketed in late 2009, the DMAA-containing OEP-OF was a popular DS formulation throughout the US until it was removed from the market in April, 2013 as the U.S. Food and Drug Administration concluded that DMAA did not qualify as a dietary ingredient, as the agency was not aware of any reliable data demonstrating that the molecule exists naturally in plants [71]. At this time, three new OEP products came on the market, in which DMAA was replaced by aegeline (OEP-NF I-III) [2,3,72].

**Epidemiological data:** The results of a nested case-control study conducted in 2012 were reported, which examined the potential risk for liver injury amongst other adverse medical outcomes (i.e., cardiac dysrhythmia, heat injury, seizure, rhabdomyolysis, cerebral hemorrhage and acute kidney failure) in 1,789 soldiers that responded to surveys exploring their use of DMAA-containing products [73]. The study population consisted of active duty army soldiers who had received treatment at a military medical facility or outsource healthcare provider from January 2011 to December 2011. Potential cases for liver injury were identified by a hospital diagnosis of relevant International Classification of Diseases, Ninth Revision, Clinical Modification codes acute/subacute necrosis of liver (570.XX). The results showed that those consuming DMAA had approximately 40% lower risk of an adverse medical outcome (of which acute/subacute necrosis of the liver was included) prior to adjusting for confounders. However, even after adjusting, the risk was 0.85, demonstrating the lack of an increased risk for adverse medical outcomes, including liver injury with DMAA used compared to no use (i.e., at 95% confidence intervals, the odds ratios were 0.63 OR, CI [0.47, 0.84] and 0.85 OR, CI [0.59, 1.23], respectively).

Thus, unlike known hepatotoxic agents which have been studied in case-control studies which demonstrated very high odds ratios consistent with a causal relationship [74-76], DMAA was found to effectively have a null effect with no increased risk of adverse medical events, including liver injury (i.e., odds ratio of 0.85) compared with no use [73].

While the authors did find a significant association between 2 or more adverse medical events with DMAA use, due to the small sample size, the odds ratio was not subjected to adjustment for confounders [73]. Thus, whether this association would remain after adjustment is unknown. The incongruity of the notion that cases who consumed DMAA were no more likely to experience each individual adverse event, yet were more likely to experience 2 or more of these same adverse events, points towards confounding as being likely. Indeed, such results may be explained by the use of any supplement in the category of sports performance or weight loss and behavior/alcohol consumption. For example, one study in military personnel found that those using ergogenic supplements were more likely to drink alcohol, ride in a vehicle with someone who had been drinking alcohol, drive after drinking and have been in a physical fight [77]. Such behavior is more likely to explain a broad increase in the risk of multiple adverse events, rather than DMAA when it demonstrated no increased risk for each individual event. Another study in military personnel found that users of dietary supplements in the categories of bodybuilding, weight loss, and performance enhancement were more likely to be overweight or obese, heavy drinkers and users of anabolic steroids in their lifetime [78]. Finally, the authors also noted that individuals reporting the most frequent use of DMAA-containing supplements (i.e., more than 80 days) were also more likely to have experienced 2 or more adverse medical events, although these data were again unadjusted for confounders. Once again, these results are most likely due to confounding by behaviors displayed in

those using central nervous system stimulants such as DMAA-containing supplements and caffeine-containing "energy drinks". For example, energy drink consumers are more likely to consume alcohol with those reporting frequent (i.e. 52 or more days) energy drink use, more often meeting criteria for alcohol dependence [79]. Data have also shown that energy drink consumers had a higher use of prescription stimulants and analgesics and demonstrated greater impulsive and sensation-seeking behavior [79]. Others have found that energy drink consumption was associated with greater heavy episodic drinking, weekly drunkenness and experiencing negative alcohol-related consequences more often [79]. Confounders such as alcohol and caffeine are better explanations for the discrepancy between the lack of individual adverse medical events and those reporting 2 or more adverse medical events.

**Pharmacological and physiological effects of DMAA:** Klontz, et al., rather than questioning their hypothesis of aegeline or OEP-NF-induced hepatitis, seem to suffer from conformational bias, concluding that DMAA or the DMAA-containing OEP-OF may also be hepatotoxic, despite acknowledging that there were no published cases of liver injury related to DMAA [2]. The authors then speculate that since DMAA has physiologic actions on the body that are similar to amphetamine, which can cause liver toxicity, this must indicate that DMAA could also cause hepatotoxicity [2]. However, the Marsh paper cited by Klontz, et al., does not support this broad assertion that DMAA and amphetamine have similar physiologic actions [2]. The paper in question evaluated the pressor or blood-pressure-raising effects of DMAA in dogs after intravenous injection [80]. While it is true that DMAA displayed a similar pressor effect to amphetamine in these dogs after intravenous administration, this type of study does not allow one to conflate the similarity of pressor effects with the similarity of other physiologic actions. For example, other molecules such as tyramine (found in fermented foods), phenylephrine and pseudoephedrine, the latter two being over the counter (OTC) drugs used to treat sinus congestion, also have pressor activity that is at least as great if not substantially greater than that of amphetamine and ephedrine yet they are not known to cause liver injury [81]. Thus, this, of course, does not mean that they share other physiologic actions of amphetamine. This finding simply demonstrates that DMAA may have alpha-adrenergic activity via direct (i.e., alpha adrenergic agonism) or indirect (i.e., increasing norepinephrine turnover) mechanisms. Furthermore, amphetamine use is considered a very rare cause of liver injury typically requiring an overdose before toxicity is seen [82]. More importantly, however, this single shared physiologic action (i.e., vasopressor effect) is irrelevant to liver injury as there is no evidence that amphetamine causes hemodynamic alterations to liver blood flow in cases of intoxication [83].

Additional evidence also undermines this claimed similarity between DMAA and amphetamine. First, the two have only superficial chemical similarities; DMAA lacks the phenethylamine skeleton found in amphetamine, showing greater similarity to aliphatic secondary amines found in various foods [84-86]. More importantly, DMAA's pharmacology is also distinct from amphetamine, which may be at least partially related to the fact that DMAA lacks the phenethylamine skeleton [87,88]. Iversen, et al., performed *in vitro* assays evaluating the potency of various compounds as inhibitors of monoamine uptake at human cloned transporters (i.e., norepinephrine transporter-NET, dopamine transporter-DAT and serotonin transporter-SERT) [89]. Amongst the compounds evaluated were DMAA and amphetamine. These data showed distinct pharmacological profiles with DMAA being inactive (i.e., Ki greater than 10,000 nmol) for DAT and SERT while demonstrating a Ki of 649 nmol for NET. This is in contrast to amphetamine, which demonstrated rather potent Ki values of 109 nmol and 101 nmol for DAT and NET, respectively, along with a Ki value of 5,728 nmol for SERT [89]. Such data actually place DMAA in a similar category (i.e., selective targeting of NET) to compounds such as pseudoephedrine [90]. Pharmacokinetic data in humans suggest that the peak plasma concentration reached after a 25 mg dose of DMAA (i.e., approximately 664 nmol) approximates the Ki for NET inhibition which, while speculative, suggests that an indirect mechanism could be involved [91]. On the other hand, Bloomer, et al., failed to detect any changes in epinephrine or norepinephrine after oral administration of up to 75 mg of DMAA in humans [92]. Thus, this appears to be an area which deserves further study.

**Randomized controlled trials:** While interesting, *in-vitro* data is considered a lower form of evidence compared to analytical epidemiology studies and randomized controlled trials [4-6]. Various randomized controlled trials in humans have been performed on DMAA alone, in combination with caffeine or in finished formulations for periods of 8, 10, and 12 weeks with markers of liver function/toxicity (e.g., ALT, AST, gamma-glutamyl transferase or GGT and bilirubin) demonstrating no significant increases from baseline or between the active and placebo conditions [1,93,94]. A 2-week study also revealed similar findings [95]. While these studies did not consist of a large subject number (e.g., the largest study consisted of 50 subjects), the total number of subjects examined and the lack of any change is worth consideration.

**Animal studies:** While Klontz, et al., have suggested that DMAA is hepatotoxic based upon a single shared physiologic action (i.e., a vasopressor effect) with amphetamine in dogs [80], other animal data fail to show similarities. For example, in a study by van der Schoot, et al., examining the locomotor effects of various compounds in mice, amphetamine was used as a positive control and demonstrated a score of 100 for locomotor activity, while methamphetamine produced a score of 168 [96]. In comparison, DMAA exhibited a score of < 3, which was the lowest score possible other than being inactive; this score was the same as beta phenethylamine or PEA, a compound found in chocolate and sold as a dietary supplement [96]. A more recent study by Dolan and Gatch confirmed the findings of van der Schoot, et al., in mice, demonstrating not only a lack of any locomotor stimulating effects but an unexpected depressant effect when compared to a vehicle control [96,97]. The authors also noted the similarity of effects produced by clonidine, an alpha 2-adrenergic agonist (which also is not amphetamine-like) and DMAA. Specifically, clonidine is known to induce locomotor depression, substitute for the discriminative stimulus effects of cocaine, partially substitute for methamphetamine and produce conditioned place preference, which is what DMAA demonstrated [97]. While the comparison of DMAA with an illicit substance such as cocaine and methamphetamine and the ability of DMAA to partially or completely substitute for their discriminative stimulus effects indicates it has, "abuse liability" or the potential for the compound to be addictive, this again does not indicate pharmacological similarity. As already noted, clonidine, an FDA-approved anti-hypertensive agent, which is not amphetamine-like also displays these effects. Furthermore, caffeine also demonstrates between 60 to 77.5% substitution for the discriminative effects of cocaine again demonstrating that while it may be addictive, it is not an indication of substantial pharmacological similarity [98,99].

More direct evidence in animal models is also available. For example, a study by Zovico, et al., examined amongst other variables, liver injury markers (i.e., ALT, AST and GGT) in male Wistar rats given OxyELITE Pro with DMAA orally by gavage at doses of 12.9 and 25.8 mg/kg, which the authors deemed to be equivalent to a human dose of 3 and 6 capsules, respectively [100]. At the conclusion of the 4-week study, the authors found no significant increase in any of these markers. Interestingly, out of the two markers for oxidative stress in the liver (i.e., Thiobarbituric acid reactive substances or TBARS and advanced oxidation protein products or AOPP), TBARS was decreased by 43% in the 12.9 mg/kg group and 25% in the 25.8 mg/kg group and AOPP was decreased by 39% and 45% in the 12.9 and 25.8 mg/kg groups, respectively, indicating the product may have anti-oxidative effects. This is in stark contrast to the effects upon the liver seen with amphetamines in rats [101,102].

**Overdose and poisoning data:** While case reports are considered the lowest form of evidence, in the case of overdoses, they may allow one to make for useful comparisons if a compound and its adverse effect follow a typical monotonic dose-response curve [103]. In this particular case, while amphetamine and amphetamines, in general, are known to cause hepatotoxicity, especially in cases of abuse or overdose [82], all of the published cases (including 50 cases in Australia and 56 cases in Texas) of DMAA intoxication or poisoning from abuse/overdose of DMAA alone or DMAA-containing products to date, lack any findings of liver injury [68,104-106]. In some cases, individuals are thought to have possibly consumed quantities of DMAA that were well beyond (i.e., DMAA plasma concentrations reported in some cases of overdose were 19-37 times higher than a 25 mg dose, which was close to if not slightly greater than the amount consumed in a single serving of most supplements) the recommendations of manufacturers [107].

## RESULTS AND DISCUSSION

### Descriptive Epidemiological Studies

**U.S. Food and Drug Administration's MedWatch Reporting:** Klontz, et al., reported 114 adverse event reports (i.e., MedWatch reports) received from February of 2012 to February of 2014, where OxyELITE Pro had been reportedly ingested, 55 of which were determined to be cases of liver disease likely due to OEP [2]. However, only 22 identified whether the formula had DMAA or aegeline in the product, indicating that 12 contained DMAA, 9 contained aegeline and 1 case indicated both formulas. Klontz, et al., surmised that aegeline in the reformulated versions of OEP was most likely responsible for the reported cases. The implication of aegeline seems reasonable considering it is the only ingredient, other than yohimbine and caffeine, found in the three marketed, DMAA-free versions of OEP. However, the fact that only 22 of 55 cases identified the ingredients, while the majority (i.e., approximately 55%) had used only DMAA-containing formulas is particularly problematic if the hypothesis is that the aegeline and "new formulas" or OEP-NF (I-III) were the cause of these liver injury cases if the majority were actually using the DMAA-containing formula. Conversely, the notion that DMAA is hepatotoxic is also problematic

if approximately 45% of cases consumed a formulation in which DMAA was absent. Furthermore, it appears that 53 of 55 (~96.3%) cases attributed by the authors to OxyELITE Pro came after public announcements, indicating potential stimulated reporting [8,9,108-112]. Indeed, the notion that stimulated reporting occurred has been indicated by others at the FDA, who noted that the reporting by the Hawaii state epidemiologist of a connection between OEP and liver injury resulted in a large number of reports being received by FDA which consequently associated the supplement with liver injury [113].

**Aegeline as the Culprit:** Despite contradictorily implicating DMAA, Klontz, et al., ultimately conclude that aegeline was the agent which caused the purported outbreak of liver disease [2]. Aegeline was the only ingredient, other than caffeine and yohimbine, found in all three DMAA-free formulations and was according to Klontz et al., introduced to the market in April of 2013 shortly before the earliest date for onset of illness, which the authors indicated as May, 2013 (the authors also report May, 2013 as being the latest onset for versions reported to contain DMAA-contradicting others [114]), but of course, it is also worth noting that these dates of onset for each version (i.e., DMAA and aegeline) are based only upon the minority of 22 reports, which actually indicated the ingredients of the product used, with the majority indicating the DMAA-containing version (i.e., OEP-OF).

As support for their assertion of aegeline's hepatotoxicity, Klontz, et al., cite a study in rats which found hepatic lesions, including central vein abnormalities after being fed *A. marmelos* plant material (i.e., around 1 g per rat or 5 to 6.67 g/kg of *A. marmelos* fruit) [2,115,116]. In doing so, however, the authors ignore not only critical issues with the study itself but also the fact that it is the only study ever published to date showing such an effect [21-26]. In fact, *A. marmelos* has not only shown a lack of hepatotoxicity it has numerous studies demonstrating a hepatoprotective effect (Table 1 and 2) [21-34].

**Table 1 Compilation of *in vivo* animal model studies evaluating the toxicity of *A. marmelos***

| Part of Plant and Extract | Animal | Dose and Route of Administration | Type of Study | Endpoints Evaluated | Result | References |
|---|---|---|---|---|---|---|
| Leaf (Methanol Extract) | Wistar Rat and Albino Mice | 10 g/kg p.o. | Acute (Single Dose) | Mortality | No Mortality Observed | Govinda and Asdaq [21] |
| Leaf (Aqueous Extract) | Wistar Albino Rat | 10 g/kg p.o. | Acute (Single Dose) | Gross Behaviour (4 hours) Mortality (7 days) | No Behavioral Changes or Mortality Authors Classify as Non-toxic | Sharma et al. [22] |
| Leaf (80% Ethanol) | Swiss Albino Mice | 50 and 100 mg/kg p.o. | Sub-acute (14 days) | Liver Weight & Protein Levels in Microsomal/ Cytosolic Fractions of Liver | No Significant Changes | Singh et al. [23] |
| Leaf (Aqueous Extract) | Parke's Strain Mice | 600 mg/kg p.o. | Sub-chronic (5 weeks) | ALT, AST, ALP, LDH, Bilirubin, and Histopathology | No Significant Changes. Histopathology was Normal. | Singh et al. [24] |
| Whole Plant (Methanol Extract) | Wistar Rat | 50 mg/kg p.o. | Sub-acute (7 days) | ALT, AST, LDH | No Significant Changes Compared to Control. | Khan and Sultana [25] |
| Leaf (Ethanol Extract) | Swiss Albino Mice | 500 mg/kg p.o. | Sub-acute (21 days) | ALT, AST, ALP, Total and Direct Bilirubin and Histopathology | No Significant Changes Compared to Control. | Sumitha and Thirunalasundari [26] |

**Table 2 Compilation of *in vivo* animal model studies evaluating the hepatoprotective activity of *A. marmelos***

| Animal | Dose and Route of Administration | Length of Study and Hepatotoxic Agent | Hepatoprotective Indicators | Result | References |
|---|---|---|---|---|---|

| | | | | | |
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| Albino Rat | 100 mg/kg p.o. | Extract administered 15 days after I.P. administration of *S. aureus*. Silymarin (25 mg/kg p.o.) was hepatoprotective control. | AST, ALT, AP, Bilirubin. | A. marmelos restored AST, ALT, AP, and bilirubin to control values. Performed similarly to 25 mg/kg dose of silymarin (known hepatoprotective agent). A. marmelos also decreased TBARS and restored GSH levels. | Ramamurthy and Gowri [27] |
| Parke's Strain Mice | 400, 500, and 600 mg/kg p.o. | Extract administered for 5 weeks along with 100 mg/kg cyclophosphamide via i.p. administration. Silymarin (100 mg/kg p.o.) was hepatoprotective control. | ALT, AST, ALP, LDH, Bilirubin, and Histopathology | A. marmelos extracts either partially or completely restored cyclophosphamide-induced alterations in liver injury markers. Histopathology also revealed a better preservation of cellular architecture. At 600 mg/kg, A. marmelos performed nearly or equally as well as 100 mg/kg p.o. silymarin. | Singh et al. [24] |
| Wistar Rat | 500 mg/kg p.o. | Each extract administered for 25 days with ethanol (50 mg/kg, p.o.) Silymarin (100 mg/kg p.o.) was hepatoprotective control. | ALT, AST, ALP, Total Bilirubin, Liver Weight and Volume | A. marmelos extracts either partially or completely restored ethanol-induced alterations in liver injury markers, liver weight, and liver volume. Performed nearly or equally as well as 100 mg/kg p.o. silymarin. | Modi et al. [28] |
| Wistar Rat | Dose not explicitly given but presumably 0.2 mg/100 g p.o. | Each extract administered for 28 days, either before or after carbon tetrachloride administration (0.2 mL/100 g i.p.) | ALT, AST, ALP, Bilirubin | A. marmelos pulp and seed extracts provided approximately 80% and 70% protection from carbon tetrachloride-induced alterations in liver injury markers. | Singh and Rao [29] |
| Wistar Rat | 25 and 50 mg/kg p.o. | Extract administered for 7 days, with carbon tetrachloride (1 mL/kg p.o.) given on the 7th day. | ALT, AST, LDH | A. marmelos pre-treatment dose-dependently decreased AST, ALT, and LDH by 46-62%, 38-58%, and 37-47%, respectively. GSH and antioxidative enzymes were also restored by A. marmelos. | Khan and Sultana [25] |
| Albino Rat | 2 g/day p.o. | Suspension administered for 21 days preceded by 40 days of 1 mL of 30% ethanol p.o. Silymarin (200 mg/kg p.o.) was hepatoprotective control. | TBARS, GSH and various indicators of oxidative status. | TBARS and GSH were effectively restored to control levels after A. marmelos powder administration. Results were similar to those given 200 mg/kg silymarin. | Singanan et al. [30] |
| Wistar Rat | 440 mg/kg p.o. | Administered for 15 days concomitantly with 500 mg/kg acetaminophen (paracetamol) p.o. | ALT, AST, ALP, bilirubin, GSH, and TBARS | ALT and AST were restored by 67% (relative to control values) bilirubin and ALP, 95% and 100% respectively by A. marmelos. TBARS (83% decrease) GSH (66% increase). | Parmar et al. [31] |
| Albino Mice | 500 and 600 mg/kg p.o. | Administered for 5 days with carbon tetrachloride (2 mL/kg) i.p. given on 2nd and 3rd day. Silymarin (200 mg/kg p.o.) was hepatoprotective control. | ALT, AST, ALP | Liver injury markers were modestly reduced relative to control. Silymarin (200 mg/kg p.o.) was more effective. | Kalaivani et al. [32] |

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| Swiss Albino Mice | 500 mg/kg p.o. | Administered 500 mg/kg p.o. for 21 days preceded by 0.2 mL/kg of carbon tetrachloride for 14 days p.o. Silymarin (100 mg/kg p.o.) was hepatoprotective control. | ALT, AST, ALP, Total and Direct Bilirubin Histopathology and antioxidant enzymes | Liver injury markers and antioxidant enzymes were moderately restored relative to control. Results were similar to 100 mg/kg silymarin p.o. Histopathology revealed reduced abnormality. | Sumitha and Thirunalasundari [26] |
| Wistar Rat | 1,000 mg/kg p.o. | Administered 1,000 mg/kg p.o. for 7 days followed by a single i.p. injection of 1 mg/kg Aflatoxin B1. | TBARS and GSH | TBARS and GSH were restored nearly to control levels. | Sivanesan and Begum [33] |
| Wistar Rat | 200 mg/kg p.o. | Administered 200 mg/kg p.o. for 21 days concomitantly with ethanol. Silymarin (2.5 mg/kg p.o.) was hepatoprotective control. | TBARS, GSH, various anti-oxidative enzymes and liver histopathology. | TBARS and GSH were restored nearly to control levels as were antioxidative enzymes (e.g., SOD, catalase, and vitamin E). Histopathology also revealed significant improvement in A. marmelos group. Silymarin appeared more effective in preventing histopathological changes. | Arun and Balasubramanian [34] |

The study cited by Klontz et al. was performed by Arseculeratne et al., whose purpose was to examine various plants used in traditional medicine for hepatotoxic alkaloids (i.e., pyrrolizidine alkaloids) and to then examine those plants which were positive for organ toxicity, including the liver, kidney, and lung [115]. The data showed that *A. marmelos*, amongst other plants, caused hepatic lesions in rats [115,116]. However, Klontz, et al., neglect to consider important limitations [2]. For example, all five of the plants (which included *A. marmelos*) in the Arseculeratne, et al., article which was not expected to produce organ toxicity (i.e., plants without known hepatotoxic pyrrolizidine alkaloids) also produced indications of hepatotoxicity, while three also showed signs of renal toxicity. In effect, all six of the plants (i.e., the 1 plant which was positive for pyrrolizidine alkaloids and 5 that were not) that were examined for toxicity in rats demonstrated histopathological changes indicative of injury, including plants which are not associated with being hepatotoxic and in fact have been shown to be hepatoprotective such as *Terminalia chebula* and *Withania somnifera* [117-119]. Because the authors neglect to publish the results of the control group, it is possible that the positive results were not due to the plants, but perhaps due to the contaminated feed or some other variable.

**Inappropriate use of MedWatch Data, faulty rationale and neglected consideration for stimulated reporting:** Klontz, et al., ultimately conclude that a causal link between OEP-NF and liver injury exists due to the following:

- Liver injury was reversed after the OEP ingestion was ceased amongst those patients who did not require liver transplantation.
- Other causes of liver disease were systematically excluded.
- Results of liver biopsies cited DILI as the most likely OEP as a cause.
- There was an abrupt reduction in reported cases of liver injury among those who consumed OEP-NF following removal of the dietary supplement from the market.

Klontz et al., as Teschke and Eickhoff have pointed out, apparently failed to use an appropriate causality assessment method such as the Roussel Uclaf Causality Assessment Method (RUCAM) which would have assigned greater or lesser causality scores depending upon how quickly ALT values decreased after cessation of exposure [3]. Instead, Klontz, et al., merely concluded that out of those individuals not requiring liver transplantation, a recovery after OEP ingestion ceased serves as evidence of causality [2]. Yet, this completely ignores the fact that the normal course for those who don't require liver transplantation after experiencing hepatitis from various other causes such as drug-induced liver injury (DILI), hepatitis E, Epstein-Barr virus (EBV) and herpes simplex virus (HSV) for example is to

recover shortly after symptoms begin [120-123]. The mere fact that individuals presenting with symptoms of hepatitis recovered thereafter does not demonstrate causality for a particular agent unless of course, other potential causes were accurately and thoroughly ruled out, including concomitant dietary supplements and medications. This leads to where Klontz, et al., claimed that other causes were systematically excluded. As Teschke, et al., have pointed out, this claim is not supported by evidence. There were cases where alternative causes of DILI (drug-induced liver injury) or HILI (herb-induced liver injury) were never considered or sought out, yet were evident in the medical histories and prescription records.

Klontz, et al., indirectly demonstrated this lack of thoroughness in cases stating that "a number of cases" had physicians rule out liver injury from viruses, autoimmune and gallbladder disease, although even in those cases, Klontz, et al., neglect to report viruses and how exactly they were ruled out (e.g., whether a serology panel was used to differentiate active infection or immunity from previous infection or vaccination or use of polymerase chain reaction). Klontz, et al., while acknowledging that some patients may not have disclosed medications and/or dietary supplements they took in addition to OEP, noted that a number of patients reported using only OEP before their illness. However, they neglected to consider that there was biased reporting/stimulated reporting of these cases for OEP caused by media and regulatory reports and biased case-seeking, as the FDA searched MedWatch cases only for those associated with OEP [113,124,125]. It shouldn't be surprising that background cases which would have otherwise been considered idiopathic or due to an alternative cause were instead reported as being due to OEP. With respect to the point that results of liver biopsies cited DILI as the most likely cause with OEP as a cause; while it is true that at least some liver biopsy results indicated DILI as a potential cause [72], the few instances where OEP was indicated as a cause stemmed from the original reporting group in Hawaii who also claimed that the pathology was consistent with DMAA-induced hepatitis, a claim for which there is no evidence and contradicts the hypothesis of aegeline-induced hepatitis [72]. Such statements support a bias and show that the initial reports from Hawaii were concerned only with DMAA, which coincided with a large amount of media and regulatory attention up to and through April of 2013, despite the fact that it was unrelated to the liver [10,11,71,72,126].

Finally, the noted reduction in reported cases of liver injury amongst those who consumed OEP-NF following removal of the supplement from the market is an association that provides only spurious evidence of a causal role. First, the pattern which Klontz, et al., describes is precisely what is known to occur in cases of stimulated reporting (i.e., publicity about an adverse event gives rise to a large number of reports after the publicity, followed by a decline shortly thereafter) [108,113]. Furthermore, the assertion by the authors that removal of one variable (i.e., removal of OEP-NF from the market) and the subsequent decline in reports of OEP-NF-induced hepatitis (i.e., the second variable) demonstrates a causal role is unfounded. It should come as no surprise that the removal of one variable in a group of two, will, of course, result in the lack of any further association. For example, thimerosal, the preservative in some vaccines spuriously alleged to have been associated with autism, was removed from childhood vaccines in the US in 2001. As evidence of its lack of harm, the Centers for Disease Control and Prevention (CDC) and other agencies have pointed out that autism rates continued to increase even after thimerosal's removal from childhood vaccines [127].

One must evaluate the total rates of a condition or disease, not the two variables alleged to have an association in the first place. If the hypothesized OEP-NF outbreak were linked to only one formulation of the product or only those containing aegeline and the rates declined or ceased after that the particular product was removed, while the remaining OEP product formulations remained on the market that might be a valid indication of a link between the two. However, that is not what happened as all formulations with the name OEP were no longer on the market by December of 2013 (i.e., DMAA-containing OEP was phased out beginning in April and was available through July 2013 while OEP-NF was recalled from the market in November of 2013). For example, as an analogy to what Klontz, et al., have done, one would look at whether the number of cases of autism alleged to have been caused by thimerosal decreased after its removal from the market. The answer is, of course, affirmative as the substance is no longer available to be implicated. But this does not serve as evidence that thimerosal caused autism. Thus, the only appropriate way to assess whether OEP-NF caused hepatitis would be to compare it to the background rates of hepatitis in the population or against controls. For example what was done in the case of some non-steroidal anti-inflammatory drugs (NSAID) or the drug flutamide; drugs known to cause hepatotoxicity [74-76,128-132]. This has not been done and likely could not be done now. An alternative way to assess whether OEP-NF caused hepatitis would be to look at the total reported rates of

hepatitis before, during and after it was on the market. There would be no expected underreporting considering one is looking only at a disease, not a cause. If OEP-NF and especially aegeline were causing hepatitis, one would expect to see a rise in hepatitis cases while it was on the market and a decline, once it was off the market. As Gibbons has pointed out in his analysis, this did not happen [133]. An additional line of evidence is the fact that aegeline in the form of the product VERSA-1, was in fact on the market as early as November of 2012, yet it does not appear as though it was the subject of MedWatch reports nor was it implicated as a causal agent in cases of hepatotoxicity [133]. Furthermore, the dose used in the product (i.e., around 400 mg per serving) was more than 3 times greater than that of the OEP products.

The attempt by Klontz, et al., to indicate that supplement formulations, including those containing DMAA and aegeline as causal agents in MedWatch cases, also ignores the appropriate role (i.e., at best a hypothesis-generating tool or an alert of a potential issue) of such reports and attempts to use them in a manner for which they were never intended. As noted, by the FDA itself, MedWatch reports are not sufficient alone to assess causality [7,8]. Aside from being incomplete, they are particularly prone to stimulated reporting and bias. These issues were recognized by Faich over 30 years ago, who stated that reports of one or even many reports of adverse reactions are insufficient to confirm that a drug caused a reaction, rather reactions may have alternative causes (e.g., other drugs, an underlying disease or coincidental) [9]. Finally, Faich also noted that "medical or mass media" attention can cause stimulated reporting [9]. In the case of OxyELITE Pro, the receipt of the reports (~96.3%) came after public announcements, which described a case definition, including a timeframe (i.e., April through December of 2013) for when the "outbreak" occurred, thus it shouldn't be surprising that cases seemingly fitting the definition and timeframe were subsequently received [2,124,125].

Finally, Klontz, et al., cite a case series of hepatotoxicity associated with the product, Hydroxycut in 2009, in an apparent attempt to draw parallels to OEP-NF [129]. However, unlike the ingredients in OEP/OEP-NF and in particular aegeline and DMAA, at least some of the previous formulations of Hydroxycut contained ingredients which are known to be hepatotoxic as evidenced by *in vitro* studies, *in vivo* animal model studies, and relatively thorough case reports with RUCAM used as the causality assessment method and/or proper and transparent reporting of clinical details and serology [66,130-132,134-139]. For example, as noted previously, green tea and EGCG, in particular, has demonstrated toxicity to hepatic cells (HEPG2) at concentrations as little as 100 μmol using a non-MTT based method, while importantly also showing toxicity in normal cells, and has shown dose-dependent indications of hepatotoxicity in animal models [66,130-132,133]. The hepatotoxicity of green tea and EGCG in human cases is also well-established [133,134]. Furthermore, *Garcinia cambogia*, another ingredient in that and an additional formula that was later implicated in causing hepatotoxicity also has animal model data and strong case reports (i.e., using RUCAM and relatively thorough and transparent case data) indicating potential hepatotoxicity [135,138,139].

Furthermore, the case series of Hydroxycut associated hepatitis from 2009 was the result of data mining of safety reports by the FDA, which demonstrated an unusually high proportion of liver toxicity associated with Hydroxycut [113,129,140]. This signal then caused investigators at the FDA to analyze clinical records of those patients who consumed Hydroxycut in order to ascertain the likelihood of causality [113,129,140]. This is in stark contrast to the case of OEP, which had no signals indicating an unusual proportion of liver toxicity being associated with the product prior to claims originating from Hawaii [2,113,140]. In fact, the entire notion of an association between OEP and liver toxicity originated not from the FDA, but from Hawaii, where officials contacted the FDA about a claimed "outbreak", followed by public announcements regarding a claimed link between OEP and liver injury [2,113,140]. As noted previously, 53 of 55 reports received by the FDA related to OEP and liver injury occurred after public announcements originating from Hawaii, which claimed an association between OEP and liver injury [2,113,140]. The remaining 2 reports were received by the FDA prior to OEP-NF being on the market and are the only reports noted from the time OEP was on the market in 2009 until the "outbreak" in 2013 (i.e., 2 reports over a nearly 4 year period). This corresponds well with a public warning in July of 2013, which noted that there were 86 reports of adverse events received by the FDA in 2012 for all DMAA-containing products (i.e., which includes OEP-OF), none of which involved liver injury [71]. The publicity likely caused retrospective analysis of cases for any adverse events in which a patient might have reported using OxyELITE Pro and likely caused those individuals and/or their healthcare professionals to report these events to the FDA, especially those fitting a defined timeframe from public reports. There were no pharmacovigilance safety signals (e.g., Empirica) during this time as well demonstrating a lack

of any number of cases beyond that expected from background [113,140]. Finally, the fact that DMAA-containing supplements remained on the market after 2013 and continue to remain on the market today, without reports of liver injury, further demonstrates the unlikelihood of DMAA being hepatotoxic [141].

**Hawaii Department of Health**

While aspects of this investigation have been covered elsewhere, it is worth noting that the narrow and flawed case definition which included only dietary supplements used for "weight loss and muscle building" when combined with a highly popular product in those defined product categories (i.e., OEP accounted for approximately 43% of total sales in Hawaii from January to September, 2013), likely led to an over-representation of OEP cases, even if it played no causal role [3,125]. While the authors do acknowledge that widespread media exposure could have caused reporting bias and limited identification of other dietary supplements as causal agents, also indicating that they did indeed identify cases of idiopathic hepatitis with OEP-NF exposure, they ultimately conclude that because OEP-NF was the only commonality, it must have been the cause [125]. Yet, this ignores that 29 cases out of 44 (66%) were consuming either a supplement other than OxyELITE Pro or in addition to OxyELITE Pro. While these other supplements were apparently distinct enough that the number of cases for the same product wasn't apparently appreciable (i.e., these data are not reported by the authors), this does not rule them out as a cause. Certainly, there are enough distinct weight loss products which contain *Garcinia cambogia* and green tea extracts which could contribute to hepatotoxicity [130-132,135-139]. Furthermore, this doesn't consider the role of other alternative causes (e.g., viruses, over the counter and prescription medications) which do not appear to have been effectively ruled out [3]. In effect, the authors conclude that since no other supplement had as many cases in aggregate as OxyELITE Pro, it must have been the cause. Yet, as discussed, the extreme popularity combined with a narrowly defined case definition (i.e., only weight loss and muscle building products), the retrospective case seeking only for OxyELITE Pro and publicity linking OxyELITE Pro to liver injury can explain the higher number of cases in aggregate.

In effect, their basis for a proposed association between OEP and hepatitis was based entirely on the lack of any other commonality amongst cases. Such a conclusion ignores the fact that the narrow case definition and product popularity likely created an over-representation of OEP cases while also neglecting the fact that the reporting bias the authors concede to as a potential factor, likely caused individuals with unique causes of hepatitis to report due to their common use of OEP. The analysis by Teschke and Eickhoff noted this exact finding, with case-patients all suffering from various and unique causes of hepatitis. This is especially likely considering that alternative causes were not systematically ruled out and were left entirely to the discretion of each individual physician treating the patient [3]. Yet, if DILI/HILI is a diagnosis of exclusion, this is unacceptable [3]. It places not only a tremendous amount of faith in the treating physician to exclude all potential causes, but also in the individual being questioned regarding their knowledge of the patient's history of OTC or prescription drug use and what, if any of those drugs may be known to cause hepatitis. Such instances, where a given condition (e.g., hepatitis) is erroneously attributed to a single cause or agent amongst a group of individuals is referred to as a "pseudo-outbreak" or "pseudo-epidemic" and is known to be caused by publicity or media exposure [142-145]. In this case, it consisted of an artefactual cluster of individuals with hepatitis causes that were unrelated. Aside from publicity or media exposure, the recent change in the liver transplant center from Hawaii Medical Center East in 2012, to Queens Medical Center (QMC) may have also played a role [146]. Interestingly, the authors found that 75% of cases reporting had consumed OEP-NF, which contradicts the findings of Klontz, et al., [2] which found the majority had consumed OEP-OF (~55%).

**Lack of Pharmacovigilance Signals**

While not considered by Johnston, et al., the notion that a greater rate of adverse event reports as a result of greater use for a given product is well-known, which is the reason one may calculate reporting rates based upon the number of reports divided by the number of sales in order to look for potential signals, although, this would need to have been calculated prior to media and regulatory publicity in order to avoid the effects of publicity and stimulated reporting [109-112,125,147,148]. The fact that a greater number of reports could be found with a compound or product that has a greater rate of use despite being no more likely to cause a given adverse event has been pointed out previously by others [147]. This is why calculating a reporting rate (i.e., number of reports divided by number of sales) is important as it provides a way to account for greater use or popularity and make for comparisons to other compounds or products as a means of identifying a potential "signal" for a given adverse event (i.e., proportional reporting ratios or PRRs) [148].

Unfortunately, this method is vulnerable to stimulated reporting via publicity [109-112,148]. However, methods for determining a PRR for OEP products performed prior to public announcements would have been useful to determine if there were any signals indicating potential hepatotoxicity. Indeed, as noted, there were no pharmacovigilance signals identified by the FDA prior to the public announcements [2,71,113,140]. This can be contrasted with the case of Hydroxycut associated hepatitis from 2009, which was discovered as a result of researchers identifying a high proportion of liver injury (i.e., a signal) from the product after mining safety reports [113,140]. Instead, the notion of an association between OEP and liver injury stemmed entirely from Hawaiian officials who announced a claimed association between the two [113].

**Centers for Disease Control led Report**

The CDC-led investigation suffers from many of the same issues as that led by the Hawaii Department of Health [124,125], including the lack of thorough and complete exclusion of alternative causes (i.e., the authors indicate an association between OEP and hepatitis despite incomplete medical records); the same exact narrow and flawed case definition which included only "weight loss and muscle building supplements" while neglecting to consider the popularity of OEP which would have inherently resulted in an overrepresentation of cases relative to other weight loss supplements, and a lack of confirmation that an outbreak had truly occurred due to a lack of an identified background rate, despite the odd occurrence of a reported "cluster" occurring only in the state of Hawaii, with the majority of sales taking place on the mainland of the United States. Additionally, the retrospective case-seeking which targeted only OEP is also a biased and problematic approach which could have contributed to such skewed results [10,11,124]. Just as with Johnston, et al., this group similarly neglects to consider pharmacovigilance principles in their analysis [125].

Perhaps one of the more glaring issues regarding the methods employed is the retrospective case-seeking which took place after OxyELITE Pro had already been implicated as a causal factor in acute hepatitis. In fact, media reports and regulatory announcements occurred on September 5, 2013, and September 26, 2013, respectively, which falls within the period for the case definition [2,124,125,149]. Thus, it is not surprising that the month of September had the highest number of cases with onset. The retrospective nature of the case-seeking combined with a product which has already been implicated (i.e., OxyELITE Pro) may create a bias which favors reporting of any cases of acute hepatitis which also happened to have been exposed to OxyELITE Pro. Furthermore, the narrow case requirement that patients must have consumed a weight loss or muscle building supplement (i.e., a description which fits OxyELITE Pro) is also extremely problematic. For example, when considering that 62.5% of reported cases patients consumed some form of OxyELITE Pro, this may simply reflect the popularity of the supplement in the category of "weight loss and muscle building" supplements. Indeed, as noted by Johnston et al. [125] from January 2013 to September 2013 in the state of Hawaii, an average of 6,912 units were sold monthly in the category of weight-loss supplements; OxyELITE Pro constituted 43% of those units, demonstrating that it was an extremely popular product. If a case definition seeks to identify supplements in which a category (i.e., weight loss) is overrepresented by a particular product (i.e., OxyELITE Pro) both due to popularity and potential bias from media and regulatory publicity, it should not be surprising that it would comprise a larger percentage of cases, even if it played no causal role. Yet, this was not considered by the authors.

Finally, Chatham-Stephens, et al., noted that out of the 35 individuals with available race data, 25.7% reported their race as Asian [124]. The authors speculate that this could be a reflection of Asians simply using dietary supplements at a greater rate, noting that one national survey found Asians had the highest rate (24.6%) of supplement use, or it could represent a greater susceptibility to liver toxicity. In this particular case, however, it is not a question of whether Asians are more susceptible to DILI in general, but whether they are more susceptible to a particular agent, in this case, OxyELITE Pro. This seems unlikely considering that a significant portion of individuals reporting were also white. Klontz, et al., also reported that out of those indicating race/ethnicity, the majority (18%) were non-Hispanic white [2]. Finally, as others have noted, the few cases from the mainland or the continental United States have included all racial groups [150]. Chatham-Stephens, et al., also reported that the median body mass index (BMI) was 28.0 $kg/m^2$ with a range of 20.6-43.1 and 81.3% of case-patients being categorized as overweight or obese [121]. The notion that overweight and obese individuals are more likely to use weight loss supplements is not surprising [151,152], but may represent an additional confounder both directly, as obesity is associated with non-alcoholic fatty liver disease which may increase susceptibility to DILI and indirectly as other weight loss supplements contain green tea and *Garcinia cambogia;* obese adults in the United States are also known to use prescription medications,

including those for hypertension, lipid-lowering, analgesia and diabetes more frequently than normal weight adults [153,154]. The notation by Chatham-Stephens, et al., that Asians may use supplements at a greater rate than others has also been confirmed by several other groups, who have found higher rates of supplement use by Asians/Hawaiians/Pacific Islanders as well as higher rates of green tea use [124,155-158]. Finally, the initial "outbreak" cases in Hawaii consisted of a significant number of Asians and Pacific Islanders, which was only later confirmed to be representative of the normal racial distribution of the population [125], however the initial publicity noting this racial representation could have subsequently led to biased reporting for those ethnicities as well.

To the authors' credit, they do note that their case finding efforts via MedWatch and the National Poison Data System focused only on OEP as a potential limitation and resulted in an overrepresentation of cases as using OEP. Other issues include the reliance upon self-reporting for alcohol, medication and dietary supplement use [159-168], the lack of actual medical records examined by the authors and the failure to assess the number of cases of idiopathic hepatitis for comparison [3,72,169]. Perhaps owing to the lack of product differentiation, the authors do not seem to indicate which formula they believed was responsible for these cases.

**U.S. Military Cases**

A brief discussion regarding the publication and reporting of the cases of Foley, et al., in the context of available epidemiological data is warranted [69]. For example, with survey data indicating an average of 22% of respondents in the army and air force having used DMAA-containing supplements and 10% of respondents indicating the use of at least once weekly, it is clear that DMAA-use in the military was significant [170]. Around 13.4% of Army respondents also indicated using DMAA in a DoD case-control study in 2011 with the highest percentage of around 5% of users indicating frequent use (i.e., 80 or more days in 2011) [73]. Yet, despite such widespread use of DMAA-containing supplements since at least 2006, there were no pharmacovigilance safety signals related to liver toxicity and no published cases of DMAA-induced hepatotoxicity prior to public reports implicating a product (i.e., of which there were formulas with and without DMAA) as a cause of hepatotoxicity in late 2013 [2,68,70,71,113,140].

**What Actually Occurred?**

**No evidence of hepatotoxicity or a true outbreak:** In this particular case, what exactly transpired may never be fully understood. However, considering the evidence to date, it is unlikely that OEP-NF or OEP-OF is hepatotoxic and that it caused an "outbreak" of hepatitis. In order for one to believe the contrary, they must believe that four different formulations with the name "OxyELITE Pro", containing four entirely different sets of ingredients (with the exception of aegeline in three of them and caffeine and yohimbine in all four) somehow caused hepatotoxicity not because of any individual ingredient but through an undetermined and unverified interaction between all of the ingredients in each formula. They must further believe that OEP-NF caused a cluster of hepatitis only in the state of Hawaii, despite the majority of sales taking place in the mainland United States and that somehow all formulas managed to evade pharmacovigilance surveillance for several years until an "outbreak" occurred which only came after publicity and public announcements of a claimed association. Multiples lines of evidence demonstrate that DMAA is not hepatotoxic [1,73,93-95,100]. Aegeline itself has been evaluated *in vitro* at extremely high concentrations and in rats without evidence of hepatotoxicity [54]; it also was recently evaluated in an observational study (ecological) by Gibbons, who found no increase and in fact a decrease in the number of cases of liver failure and acute hepatitis during the time aegeline was on the market just before the public announcements purporting that OEP-NF was associated with liver injury [133]. There was also no dose-response relationship found. Gibbons also points out that the rate of reported liver injury in Hawaii which was attributed to aegeline or OEP-NF was 186 per 100,000 [133]. He also interestingly determined a background annual rate of 18 per 100,000, which compares well to the estimated incidence of DILI at 19 per 100,000 in Iceland [171]. In any event, Gibbons notes that if the rate of hepatitis cases in Hawaii were applied to the total number of sales for the products, there would have been an additional 2,133 cases of acute hepatitis and liver failure in the United States, which obviously did not happen [133]. If the background rate of 18 per 100,000 were applied to the number of total OxyELITE Pro sales, while also assuming that the two populations experience acute hepatitis and liver failure at a similar rate, there would be approximately 218 cases amongst consumers which would have occurred regardless of whether they took OEP or not, although this is clearly speculative [133]. To further confound matters, some evidence suggests that counterfeit OEP may have been introduced to the market, with unknown contents and/or drugs [14]. If or how this could have affected the reporting of hepatitis associated with OEP

is unknown; while chemical analysis of available products failed to reveal substances other than what was on the label [2,124,125], the products used by patients were not always available to be analyzed [3]. However, even if there were counterfeit versions which caused liver injury, the number would be expected to be small (i.e., otherwise evidence of a true outbreak would be seen, yet there is none [133,147]) with a pseudo-outbreak and stimulated reporting likely responsible for most of the reported cases [133,147]. However, the notion that a small number of initial cases due to counterfeit products could have served as an impetus for a pseudo-outbreak and stimulated reporting is also possible.

**A Genetic Predisposition?**

Some have indicated that the significant number of Asian and Asian Pacific Islanders in Hawaii, which reportedly experienced hepatotoxicity from OEP-NF/OEP is an indication of an ethnic or genetic susceptibility and that this could explain why there was only a cluster in Hawaii, despite the majority of sales taking place in the mainland United States. However, as Johnston, et al., noted, after controlling for differences in data collection methods, the racial background of the cases was not significantly different from the normal racial representation found in Hawaii [125]. Furthermore, in a study evaluating cases of autoimmune hepatitis (AIH) in Hawaii, the authors found that the majority of individuals diagnosed were females of Asian descent, which was simply thought to reflect the normal distribution in the Hawaiian population [172]. Klontz, et al., and Chathem-Stephens, et al., also found that non-Hispanic whites actually comprised either a significant portion or majority of the reported cases, while others have noted the cases in the mainland U.S. have consisted of a mix of all races [2,124,150]. Thus, if there is no unique genetic factor which explains why there was only an apparent cluster in Hawaii when combined with additional evidence, it supports the notion that OEP-NF/OEP is not hepatotoxic.

**A Pseudo-Outbreak is Most Likely Responsible**

While the evidence to date does not support the notion that OEP is hepatotoxic, it does indicate that the name "OxyELITE Pro" was clearly and effectively communicated as being associated with liver toxicity, resulting in an association with any product displaying that name. Thus, the name, rather than any specific formulation or ingredient was associated with hepatotoxicity, making the claimed association artefactual resulting in a "pseudo-outbreak" characterized by an artefactual cluster of individuals with various unrelated causes of hepatitis as noted by Teschke and Eickhoff [3]. The work of Gibbons as well as the fact that the number of transplants performed and individuals listed for transplants in Hawaii during the 2013 year was well within a normal historical range also demonstrates the lack of any true outbreak [133,147]. While speculative, ultimately, this pseudo-outbreak may have begun with the observations of a single physician at QMC, who may have been biased by previous experiences with a weight loss product (i.e., Hydroxycut) associated with hepatitis as well as recent media attention involving DMAA around and before April, 2013 [10,11,71,126], while neglecting to consider the historical rate of liver transplant candidates seen annually [146,173]. When confronted with what she believed to be an abnormal number of cases requiring assessment for liver injury, this previous knowledge may have caused bias and led to her actively seek out a commonality amongst these patients [173]. Unaware of the popularity of OEP, this physician could not have known that more than 40% (4 out of 10) of individuals having used a weight loss supplement were likely to have used OEP. Upon finding one or more cases, which had reported also using OEP, this staff member appeared to immediately conclude that it was causal, leading to statements that the histopathology of the liver in at least some cases was "consistent with DMAA" induced liver toxicity, despite the fact that there is no such existence for a DMAA-type liver pathology [72]; contradictorily, this same case-patient data and histopathology would later be used to substantiate a claim of hepatotoxicity from the DMAA-free formula, OEP-NF [3,72,174]. After alerting the media, this likely caused additional cases to report, which also happened to be using different formulations with the name, OxyELITE Pro, ultimately causing stimulated reporting and a "pseudo-outbreak". Two of the known causes of pseudo-outbreaks were present in this case. Specifically, there was an "increased interest because of local or national awareness" or "media publicity" and "a new physician or healthcare facility" which "may more consistently report cases" [142,143,145]. Clearly the media attention in Hawaii and national attention comport with an "increased interest because of local or national awareness" of the supposed link between OEP-NF/OEP-OF and hepatitis, which likely caused stimulated reporting and there was also a change in Hawaii's sole liver procurement and transplant hosting center which fits the change in physician/healthcare facility. Prior to 2012, the Hawaii Medical Center East was the sole liver procurement and transplant hosting center for the state of Hawaii, where it had such a designation from 1993 through 2011 [146]. Starting in 2012, the Queen's Medical Center became the sole liver procurement and transplant hosting center. The

main physician who is credited with "discovering", this so-called outbreak commented that she believed the number of cases she encountered seemed higher than expected [173]. However, evaluating the number of transplants and individuals added as candidates for transplant in Hawaii (Table 3) as reported by the United Network for Organ Sharing (UNOS) fails to reveal any abnormal numbers in 2013 versus other years with the results all falling within one (or in one case two) standard deviations of the mean [146].

**Table 3 UNOS liver transplant data for the state of Hawaii from the years 1993 to 2016**

| 1993 to 2016 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TT | 3 | 2 | 1 | 4 | 7 | 9 | 9 | 11 | 9 | 11 | 12 | 15 | 14 | 11 | 12 | 13 | 17 | 16 | 16 | 11 | 12 | 15 | 13 | 17 |
| AHNT | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 4 | 6 | 5 | 2 | 2 | 3 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 3 | 1 | 1 | 0 |
| CLTT | - | - | 5 | 10 | 10 | 14 | 20 | 19 | 15 | 18 | 17 | 20 | 33 | 25 | 21 | 27 | 14 | 24 | 18 | 28 | 35 | 18 | 30 | 25 |
| CLT- AHN | | | 0 | 0 | 0 | 0 | 1 | 12 | 11 | 13 | 0 | 1 | 3 | 1 | 1 | 1 | 1 | 3 | 2 | 1 | 6 | 0 | 3 | 1 |
| TT=Total transplants performed; AHNT=Transplants performed with a diagnosis of acute hepatic necrosis; CLTT=Candidates listed for a liver transplant; CLT-AHN=Candidates listed for a liver transplant with a diagnosis of acute hepatic necrosis | | | | | | | | | | | | | | | | | | | | | | | | |

For example, the number of liver transplants performed in Hawaii as reported in total was 12 in 2013. However, from 1993 through 2016, there were between 1 to 17 liver transplants performed, including 15, 13, and 17 for the years 2014, 2015 and 2016, respectively, while the mean and standard deviation were 10.83 ± 4.64, 95% CI [8.98, 12.69] (Table 3). The number of liver transplants performed in Hawaii listed as being due to acute hepatic necrosis was 3 in 2013. However, from 1993 through 2016, there were between 0-6 cases with several years of between 2 to 6 cases, with a mean and standard deviation of 1.46 ±.1.67, 95% CI [0.79, 2.13]. Furthermore, the number of individuals added as candidates for a liver transplant was 35 for all diagnoses in 2013. Yet, for the years 1995 to 2016, the total numbers of candidates listed don't reveal this to be an outlier representing any sort of "outbreak". In fact, the years 2005, 2012 and 2015 had 33, 28 and 30 candidates, respectively (20.27 ± 7.61, 95% CI [17.09, 23.45]). Of those candidates, the number which had a diagnosis of acute hepatic necrosis varied from 0 to 13 (with 6 in 2013) with a mean and standard deviation of 2.77 ± 4.02, 95% CI [1.09, 4.45]. This indicates that the reporting of cases associated with OEP-NF/OEP-OF were real cases of hepatitis likely stemming from various different or unrelated causes, which were background cases that were either idiopathic or due to alternative causes, which were subsequently associated with OxyELITE Pro through stimulated reporting and retrospective case-seeking by investigators. The change in the liver transplant center and the lack of familiarity with the large variation in the number of cases which can be seen in any given year may have caused one or more individuals to misinterpret a year with a higher, but not a historically unusual number of liver cases as being an indication that something abnormal was occurring [146,173]. The fact that the reported "outbreak" coincided with an unplanned, U.S. government "shutdown" may also explain why this phenomenon (i.e., a pseudo-outbreak) went unnoticed as many public health employees were furloughed.

Indeed, the false association of various agents with disease and injury is not a new phenomenon. Pariente, et al., have used the term, "notoriety bias", to describe the specific effect of stimulated reporting in response to public announcements from regulatory agencies (e.g., in the case of OEP-NF, the Hawaii Department of Health and the FDA/CDC) about safety alerts regarding an association between a given drug or substance and a given adverse effect [109]. While it is not disputed that spontaneous adverse event reporting systems can be useful to identify potential safety signals, these signals, if appearing after publicity either in the form of regulatory announcements or media reports, may, in fact, be meaningless. Yet, even when a safety signal is generated, it must then be analyzed using established statistical methods in pharmacoepidemiology or analytical epidemiology [109]. Some have in fact noted that in some cases, dietary supplements may be the subject of over-reporting [175,176].

The fact that OxyELITE Pro did not cause liver injury and was a victim of stimulated reporting can also be seen in the data from FDA's own databases prior to the publicity. For example, Empirica, FDA's database used to detect "signals" of injury from dietary supplements, failed to reveal any signals for OEP/OEP-NF prior to the public announcements as there were effectively no cases [2,113,140]. Most recently, authors from the FDA have confirmed the likelihood of stimulated reporting, noting that the large number of reports received by the FDA occurred as a result of public reporting by the Hawaii state epidemiologist of a link between OEP/OEP-NF and liver injury [113].

Of course, there are other examples where case reports and a temporal association are later found to be due to non-causal factors. For example, a case series of postural-orthostatic tachycardia syndrome (POTS) consisting of 25

women in Denmark suggested a temporal association with a quadrivalent human papillomavirus (HPV) vaccine. A subsequent case-control study and analysis by the European Medicines Agency (EMA) found no evidence that the HPV vaccine causes POTS, with authors noting that "while temporal associations may be observed, conclusions of causality cannot be drawn from case reports and case series due to the small sample size and lack of control population" [13,177]. Similarly, immunizations were temporally associated with Kawasaki disease characterized by systemic vasculitis in many case reports. However, a systematic review of all published studies found a lack of evidence for a causal role [178]. Another example includes the use of silicone breast implants being temporally associated with rheumatoid arthritis in women receiving them, this association was eventually shown not to be causal [179,180]. Of course, it is also worth noting that in many of the cases where OxyELITE Pro was alleged to have caused hepatotoxicity, even a temporal association is questionable considering a long latency period (see cases 1 and 7 of Foley, et al., [69] and cases 4 and 5 of Heidemann, et al., [114] in Part 2) with alternative causes having a closer temporal relationship than OEP-NF/OEP.

Finally, there is a case from 2010, where an Emergency Department (ED) physician notified the CDC of a cluster of military reservists in Alabama who presented with non-specific systemic adverse events after they received an inactivated monovalent pandemic 2009 (H1N1) vaccine [181]. On the day of the vaccination (i.e., four hours after administration) one of the reservists presented to the ED with symptoms consistent with possible Guillain-Barre Syndrome (GBS). The patient was admitted to the hospital and after being attended by a neurologist was diagnosed with generalized weakness (i.e., GBS was ruled out), recovered and was released [181]. The following day, the commanding officer called a meeting with the other 200 reservists and advised them about the case of their fellow reservist, while encouraging them to report any adverse events to the ED regardless of severity. Subsequently, on that same day, 13 reservists reported to the ED with non-specific symptoms, which recovered with supportive therapy. The authors ultimately concluded that this was a case of stimulated reporting and that action taken by the commanding officer (i.e., informing other reservists of the original case and advising them to seek medical attention if they thought they had an adverse event) played an important role [181]. Indeed, it is not difficult to see the parallels with those in Hawaii, where the public was notified that OxyELITE Pro was associated with liver toxicity and to report cases to authorities or their physician. The main difference between the vaccination case and that of OEP is the former had non-specific symptoms, likely to be a cluster of unrelated cases stimulated to report coincidental effects, while the latter consisted of actual hepatitis cases but an artefactual cluster with unrelated causes, stimulated to report. In this case, 6.5% of those who received the vaccine and had been advised by their commanding officer ended up reporting adverse effects [181].

Such pseudo-outbreaks are seemingly rare, but such instances of false alarm induce panic amongst patients and are likely to cause inappropriate or insufficient treatment due to a misdiagnosis, causing emotional and physical harm [182,183].

## CONCLUSION

Ultimately, several lines of evidence suggest that OxyELITE Pro, DMAA, and aegeline are not hepatotoxic. The claimed "outbreak" that only occurred in Hawaii in 2013 was likely a "pseudo-outbreak" or "pseudo-epidemic" as a result of media and regulatory publicity, a new liver transplant facility and stimulated reporting along with retrospective case seeking efforts. The failure to rely upon accepted pharmacovigilance (e.g., signal detection) and epidemiological approaches (e.g., analytical epidemiology) along with lack of consideration for available lines of interventional data also contributed to an erroneous assumption of causality. While instances such as this are seemingly rare, the unnecessary panic and incorrect or insufficient treatment due to a misdiagnosis suffered by patients underline the need to prevent such instances.

## DECLARATIONS

### Conflict of Interest

The author has served as a consultant to USPlabs, the manufacturer of OxyELITE Pro and is a defendant in ongoing litigation related to OxyELITE Pro. USPlabs was not involved in the conception, writing, or editing of this article. The views expressed here are those of the author.

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