

Review

Steviol glycoside safety: Are highly purified steviol glycoside sweeteners food allergens?

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ABSTRACT

Steviol glycoside sweeteners are extracted from the plant *Stevia rebaudiana* (Bertoni), a member of the Asteraceae (Compositae) family. Many plants from this family can induce hypersensitivity reactions via multiple routes of exposure (e.g., ragweed, goldenrod, chrysanthemum, echinacea, chamomile, lettuce, sunflower and chicory). Based on this common taxonomy, some popular media reports and resources have issued food warnings alleging the potential for stevia allergy. To determine if such allergy warnings are warranted on stevia-based sweeteners, a comprehensive literature search was conducted to identify all available data related to allergic responses following the consumption of stevia extracts or highly purified steviol glycosides. Hypersensitivity reactions to stevia in any form are rare. The few cases documented in the peer-reviewed literature were reported prior to the introduction of high-purity products to the market in 2008 when many global regulatory authorities began to affirm the safety of steviol glycosides. Neither stevia manufacturers nor food allergy networks have reported significant numbers of any adverse events related to ingestion of stevia-based sweeteners, and there have been no reports of stevia-related allergy in the literature since 2008. Therefore, there is little substantiated scientific evidence to support warning statements to consumers about allergy to highly purified stevia extracts.

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Abbreviations: ADI, acceptable daily intake; CDC, Centers for Disease Control and Prevention; DTH, delayed type hypersensitivity; EFSA, European Food Safety Agency; FDA, Food and Drug Administration; FSANZ, Food Safety Authority of Australia–New Zealand; GRAS, Generally Recognized as Safe; kg, kilogram; JECFA, Joint FAO/WHO Expert Committee on Food Additives; mg, milligram; LTP, lipid transfer protein; SCL, SafetyCall International Poison Center; SL, sesquiterpene lactone; TLP, thaumatin-like protein; WHO, World Health Organization.

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1. Introduction

1.1. Background

Stevia rebaudiana (Bertoni) is an herbal shrub belonging to the *Asteraceae* (Compositae) family and native to Paraguay and Brazil. Historically, the stevia plant has served a number of food and medicinal uses in South America where its use can be traced back hundreds of years. In the United States and Europe, stevia is a more contemporary addition to the marketplace (Carakostas et al., 2012). Initially, crude extracts or stevia leaves were sold as dietary supplements or traditional herbal preparations (Abdel-Rahman et al., 2011). The need to precisely define and control specifications to meet regulatory requirements led to the development of highly purified extracts containing $\geq 95\%$ steviol glycosides, a group of high potency, non-caloric sweet compounds present in *S. rebaudiana* leaves (Fig. 1, Table 1).

The use of purified stevia extracts as sweeteners is currently permitted in a wide number of countries (Carakostas et al., 2012), as the safety of high purity steviol glycosides has been extensively reviewed in the published literature and by national and international

food safety agencies. Periodic reviews by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) of the safety of purified steviol glycosides has led them to conclude that stevioside and rebaudioside A are safe for consumption as general-purpose sweeteners (JECFA, 2005). JECFA established an acceptable daily intake (ADI) for steviol glycosides of 0–4 mg steviol equivalents/kg body weight/day without any qualifications in 2008 (JECFA, 2008). Similar assessments and conclusions on safety have been conducted by the European Food Safety Agency (EFSA, 2010), the Food Safety Authority of Australia–New Zealand (FSANZ, 2008) and Health Canada (2012). Since 2008, numerous expert panels in the United States have concluded that highly purified preparations of steviol glycosides ($\geq 95\%$) meet the US Food and Drug Administration (USFDA) standard for being classified “Generally Recognized as Safe” (GRAS) (USFDA, 2014).

1.2. Phylogeny and concerns of allergenicity

A number of plants from the *Asteraceae* (Compositae) family can induce hypersensitivity reactions via multiple routes of exposure: dermal, inhalation, and ingestion. Plant-derived allergens in this family include well-known respiratory allergens (e.g., ragweed, mugwort and goldenrod), contact allergens (e.g., daisy, dandelion and chrysanthemum) and ingested allergens (e.g., German chamomile and Echinacea) (Gordon, 1999; Huntley et al., 2005). Internationally, the Codex Alimentarius Commission has identified eight foods or food groups (peanut, soybean, tree nuts, cereal sources of gluten, milk, eggs, crustacean shellfish, and fish) as important allergenic sources that should be identified on product labels (Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO), 2007). These foods or food groups are responsible for 90% of all serious food allergies (FAO, 1995).

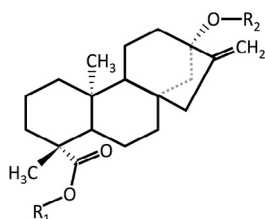


Fig. 1. Steviol glycoside – aglycone structural core.

Table 1
Chemical structures of steviol glycosides.

Compound Name	R1	R2	Sweetening potency ^a	FDA GRAS for high purity SG
Stevioside	β -Glc	β -Glc- β -Glc(2 $\rightarrow$ 1)	150–250	Yes
Rebaudioside A	β -Glc	β -Glc- β -Glc(2 $\rightarrow$ 1) $\angle$ β -Glc(3 $\rightarrow$ 1)	200–300	Yes
Rebaudioside B	H	β -Glc- β -Glc(2 $\rightarrow$ 1) $\angle$ β -Glc(3 $\rightarrow$ 1)	150	–
Rebaudioside C	β -Glc	β -Glc- α -Rha (2 $\rightarrow$ 1) $\angle$ β -Glc(3 $\rightarrow$ 1)	30	–
Rebaudioside D	β -Glc- β -Glc(2 $\rightarrow$ 1)	β -Glc- β -Glc(2 $\rightarrow$ 1) $\angle$ β -Glc(3 $\rightarrow$ 1)	221	Yes
Rebaudioside E	β -Glc- β -Glc(2 $\rightarrow$ 1)	β -Glc- β -Glc(2 $\rightarrow$ 1)	174	–
Rebaudioside F	β -Glc	β -Glc- β -Xyl(2 $\rightarrow$ 1) $\angle$ β -Glc(3 $\rightarrow$ 1)	200	–
Rebaudioside X	β -Glc- β -Glc(2 $\rightarrow$ 1) $\angle$ β -Glc(3 $\rightarrow$ 1)	β -Glc- β -Glc(2 $\rightarrow$ 1) $\angle$ β -Glc(3 $\rightarrow$ 1)	200–350 ^b	Yes
Dulcoside A	β -Glc	β -Glc- α -Rha(2 $\rightarrow$ 1)	30	–
Rubusoside	β -Glc	β -Glc	114	–
Steviolbioside	H	β -Glc- β -Glc(2 $\rightarrow$ 1)	90	–

^a Sweetness potency relative to sucrose, where sucrose sweetness potency = 1 (Carakostas et al., 2012).

^b Sweetness potency relative to sucrose estimated in USFDA GRAS Notice No. GRN 473 (USFDA, 2013).

Similarly, in the United States, these same eight foods or food groups are subject to Congressionally mandated labeling requirements under the Food Allergen Labeling and Consumer Protection Act of 2004 (NIAID-Sponsored Expert Panel et al, 2010). However, the prevalence of food allergies varies geographically, as recent EuroPrevall studies out of Europe have reported (Burney et al., 2014). Pollen allergies associated with inhalation exposures are much more common than food allergies, and allergies associated with exposure to pollens from the *Asteraceae* family (e.g. ragweed, mugwort) are quite common in many parts of the world. In some pollen-sensitized individuals, allergic reactions can occur upon the ingestion of foods or dietary supplements from the *Asteraceae* and other families that contain proteins that are identical to, or cross-reactive with, pollen allergens. This is a common condition, known as oral allergy syndrome or pollen-food syndrome, but symptoms are generally mild (Ortolani et al., 1988). Pollen-food syndrome does occur between various foods in individuals sensitized to pollens from the *Asteraceae* family (e.g. ragweed, mugwort, etc.), but most of the implicated foods do not belong to the *Asteraceae* family. *S. rebaudiana* is a lesser-known member of the *Asteraceae* family, the high purity extracts of which have been incorporated into diet at an increased rate since 2008.

Based on common phylogeny, there is a concern that extracts of *S. rebaudiana* possess allergic potential (Ulbricht et al., 2010), though there is a noticeable paucity of verifiable evidence to support this concern. Importantly, this perception appears not to be due to a significant number of documented cases, but by virtue of the fact that it belongs to a family of plants known to be commonly allergenic. As a result, food allergy warnings for stevia products in general (not differentiating between the high and low purity products) are given in some popular food information sources, and many non-scientific media reports and resources allege the potential for allergic response to any stevia-based products. For example, the New Health Guide website claims that, in rare cases, stevia can cause anaphylaxis, though such assertions lack citations to supporting peer-reviewed literature. It is also stated that those with a pre-existing allergy to members of the *Asteraceae* (Compositae) plant family may be more susceptible to anaphylactic symptoms upon exposure to stevia.¹ Other popular media, including WebMD and the LiveStrong Foundation, have reiterated this warning.^{2,3}

Notably, however, two regulatory agencies have reviewed the allergenicity potential of purified stevia extracts. In the first case, EFSA noted there were very limited data on the issue of allergy. Based on the lack of data and the extensive history of use in many cultures, plus the fact that steviol glycosides are not reactive compounds and are not metabolized to reactive compounds, EFSA concluded that “...it is unlikely that the steviol glycosides under evaluation should cause by themselves allergic reactions when consumed in foods” (EFSA, 2010). More recently, Health Canada reviewed the available literature and came to the same conclusion, noting that what little data were available to suggest a potential association between stevia and hypersensitivity was made less relevant by the fact that high purity extracts were not evaluated in any scientific or case study. Health Canada’s Food Directorate concluded, “...highly purified steviol glycosides, including purified preparations of rebaudioside A, used as a food additive are unlikely to be an allergenic concern for the general population” (Health Canada, 2012). Additionally, high purity stevia sweeteners have not been recognized as potential food allergens by Food Allergy Research & Education,⁴ a nonprofit organization coun-

seled by prominent members of the medical and research communities.

1.3. Objective

To determine if allergy warnings by health-care providers are warranted on products containing high purity ($\geq 95\%$) steviol glycoside sweeteners or if they should be listed in allergy awareness websites, a comprehensive evaluation of the scientific literature was conducted. Adverse event report information from major stevia suppliers and publicly available food-related adverse event databases were also evaluated.

2. Methods

An extensive search of the scientific literature was conducted using various databases (e.g., PubMed, Science Direct, Google Scholar) to identify any publications related to steviol glycosides and/or stevia leaf extracts of known concentrations, and potential allergic reactions. The search was conducted on October 14, 2014, and used binary combinations of the following groups of key terms: (i) “stevia,” “stevioside,” “steviol glycoside,” or “rebaudioside,” and (ii) “allergy,” “hypersensitivity,” and “reaction.” Given the paucity of results, all resulting studies were further studied for relevance. Resources on surveillance data for adverse health effects related to food consumption – including FDA, CDC, and online food allergy networks – were searched for incidents related to stevia or steviol glycoside consumption. Additionally, the results of a recent post-market surveillance study that monitored the consumer safety of a highly purified steviol glycosides based non-nutritive sweetener were reviewed and included in this evaluation (Kingston et al., 2013). This surveillance effort was conducted between 2008 and 2012 by SafetyCall International Poison Center (SCI) on behalf of Cargill Incorporated for the 2008 launch of Truvia® brand sweetener, and utilized a 24-hr/7-day/week SCI medical call center support line for U.S. consumers alleging product related adverse effects.

3. Results and discussion

The scientific literature is fairly sparse on the issue of the potential allergenicity of steviol glycosides or stevia leaf extracts in humans or animals. An extensive search yielded no studies on purified steviol glycosides or stevia leaf extracts meeting JECFA specifications (i.e., steviol glycoside extract products containing no less than 95% steviol glycosides on a dried basis; JECFA, 2010). In all, the search identified only two studies published in peer-reviewed journals that reported cases of allergy or allergy-type reactions in humans associated with the consumption of stevia products, one animal study suggestive of the allergenic potential of stevia, as well as two reviews that made statements on the potential for stevia products to produce an allergenic response upon consumption.

3.1. Evidence for stevia allergenicity in the literature: case studies

Only two case studies have reported potential allergic reactions in individuals who had consumed products containing a stevia sweetener. Kimata (2007) published a brief communication on two pediatric patients with atopic eczema and known food allergies who experienced anaphylaxis after either chewing on stevia leaves or ingesting a “stevioside powder” and water mixture. In both cases, the children recovered from their anaphylaxis after an injection of dexamethasone at the emergency room. Allergic sensitization to the stevia plant and a stevioside extract solution (10% v/v) was confirmed in each child by prick-to-prick skin test. Kimata reported that 2-month avoidance of stevia and/or stevioside-containing foods resulted in negative follow-up skin prick tests; no additional anaphylactic events were reported, and the underlying atopic eczema in each of the patients was said to improve. However, a positive skin test is insufficient to document that an allergic reaction would occur in these two individuals upon ingestion of stevia or stevia extract. An oral challenge trial or demonstration of mediator release from basophils armed with IgE antibodies from these subjects would have

¹ <http://www.newhealthguide.org/Stevia-Side-Effects.html>.

² <http://www.rxlist.com/stevia-page2/supplements.htm>.

³ <http://www.livestrong.com/article/368454-known-side-effects-of-stevia/>.

⁴ <http://www.foodallergy.org/>.

been necessary to document that stevia or stevia extract were the causes of the allergic reactions. Furthermore, these individuals may have been sensitized to one of the *Asteraceae* family pollens that could have elicited the positive skin test result without proving allergic reactivity to stevia or stevia extract.

These episodes led the investigator to conduct a broader skin prick study on 200 children to determine if atopy in young children was associated with an increased incidence in stevia allergy. This group of 4 month to 2 year olds was comprised of 50 healthy children (no reported allergies), 50 children with allergic rhinitis, 50 children with bronchial asthma, and 50 children with atopic eczema. As with the initial two patients, two prick-to-prick skin tests were conducted in each child using stevia leaves or the stevioside extract powder solution, both before and after a 2-month avoidance period of stevioside-containing foods. None of the healthy children were sensitized to stevia leaves or the stevioside mixture as all had negative skin responses. There was a tendency for those children with existing allergic conditions to yield positive responses to either of the skin prick stevia agents, as 16%, 34%, and 64% of the children with allergic rhinitis, bronchial asthma, or atopic eczema were determined to be sensitized, respectively. The rate and severity of positive reactions were reduced after the 2-month avoidance period, dropping to 6–8%, 4–6%, and 10–14%, respectively, demonstrating a loss of sensitivity to stevia leaves and the stevioside mixture in the majority of children. The difference in skin test results from extracts made two months apart is puzzling. Allergic sensitization does not usually disappear over a two-month time period. It is tempting to speculate that these two extracts were somehow different and the first extract contained some contaminating protein that was responsible for the positive skin test. Clearly, both extracts should have contained any stevia proteins or other sensitizing compounds found in the *Asteraceae* family. Since only the first extract caused a positive skin test in the index patients, this seems to rule out stevia as the cause unless allergic sensitization was unexpectedly resolved over the two-month time period.

While Kimata (2007) indicates that ingestion of stevioside-containing food may induce an allergic reaction in individuals with existing allergic conditions, this study is limited in its utility to inform the issue of high purity steviol glycosides as potential food allergens. Stevia leaves aside, the stevioside mixture used for the skin prick tests was made from stevia extract powder made by a manufacturer in Shandong, China. Kimata (2007) does not specify the purity of the stevia extract used in the skin prick tests, but the manufacturer's product guide currently only lists 80 and 90% pure stevioside powder extracts (Zibo Inchcape Industry Inc. products listed at www.healthsweet.com). (Commercial stevia sweeteners offered for sale since 2008 are generally more pure than stevia dietary supplements sold prior to this year.) The extract used in the allergy testing likely did not meet the JECFA or FDA specification for high purity steviol glycosides as food sweeteners ($\geq 95\%$), and thus may have contained impurities of unknown allergenicity. As noted above, the possible presence of some contaminant from a known allergenic plant pollen could explain the unusual disappearance of skin sensitivity over the two-month observation period.

The skin prick test, where commercial extracts are available for clinical use, is a recognized method for whole foods and extracts. However, no commercial skin test extract exists for stevia leaves or powder. The prick-to-prick method is often used in such circumstances and involves placing the end of the needle into the material and then pricking the patient's skin with this needle. However, this approach is known to administer variable levels of unstandardized test material, thus leading to false positive results as well as the potential for adverse reactions (Antunes et al., 2009). To this point, the food allergy sensitivity rate (i.e., the rate of true positive outcomes) for the skin prick test has been estimated to be approximately

85%, indicating a false positive test in one-to-two subjects for every ten subjects tested (reviewed in Kurowski and Boxer, 2008). The prick-to-prick method would be predicted to have an even higher false positive rate. As such, a food challenge test is recommended prior to allergy confirmation (Wananukul et al., 2005), an approach not discussed by Kimata (2007). Furthermore, individual histories of food allergy and prior exposure to stevia within the groups of children tested for hypersensitivity to stevioside or stevia leaves were not reported by Kimata (2007). This would be useful information for relating the results of the skin prick tests in the healthy and atopic children back to the case reports of the two children with known food allergies. Considered together, therefore, these study limitations suggest that the symptoms reported by Kimata (2007) in the initial two case reports may have been related to factors other than the steviol glycosides present in the stevia leaves or stevioside-food product. The report by Kimata cannot be considered a clearly substantiated example of stevia hypersensitivity.

The only other report in the literature of potential allergy symptoms related to stevia product ingestion is that of the case study of a 32-year old woman described by Esmail and Kabadi (2012). In this case, the patient had experienced persistent edema (in addition to hypertension and hypokalemia), during which time it was determined that she was regularly consuming a stevia powder as an herbal sweetener. Evidently she had been adding 6–8 g of the stevia powder to her coffee, of which she consumed 2–3 cups per day. At that level of stevia use (given the sweetness intensity of purified stevia sweeteners), the ingredient was very likely a low purity stevia product – perhaps even ground stevia leaves. In addition, she used the stevia powder in preparing desserts consumed on a weekly basis. Discontinued use of the stevia powder resulted in a remission of the edema and other symptoms, implicating it as the causative agent.

The patient's symptoms of edema and hypertension are not generally consistent with a diagnosis of an acute food-related hypersensitivity reaction where hypotension is more typical (Wang and Sampson, 2007). In fact much of the previous herbal literature claimed a blood-pressure reducing effect following the ingestion of stevia leaves or crude extracts (Chan et al., 2000; Hsieh et al., 2003). More recent clinical studies have shown that high-purity steviol glycoside sweeteners have no effects on blood pressure in normo-tensive or low normo-tensive individuals (Maki et al., 2008a, 2008b). Furthermore, neither the nature nor purity of the herbal "Stevia powder" was reported by Esmail and Kabadi (2012), nor was any information provided on other possible alterations of the patient's diet during the stevia powder avoidance period. Thus, this case study cannot be assumed to be evidence of hypersensitivity following ingestion of purified steviol glycosides.

Overall, the current literature is limited in its utility to identify high purity steviol glycosides as potential allergens. Conversely, the paucity of studies and limited data represent a data gap, and suggests that the potential for allergenicity cannot be absolutely ruled out. Additional studies conducted using high purity steviol glycosides and appropriate challenge-avoidance testing would help to fill this gap. The literature also lacks cross reactivity studies (e.g., immunoblot or BAT assays using steviol glycosides and serum from patients allergic to other *Asteraceae* family members). Such studies would directly address the hypothesis that individuals allergic to plants of the *Asteraceae* family might also be susceptible to ingestion of highly purified steviol glycosides.

3.2. Evidence for stevia allergenicity in the literature: animal studies

The literature search also uncovered a mouse study published by Sehar et al. (2008) as possibly related to hypersensitivity. In this

study, the impact of stevioside preparations on delayed type hypersensitivity (DTH) response was evaluated in normal and immune-compromised mice. Normal and cyclophosphamide-treated mice were further split into three dose groups, a vehicle control group, and a cyclophosphamide control group. Oral doses of 6.25, 12.5, or 25 mg stevioside/kg body weight were administered daily over a 7-day period. The mice were immunized with sheep red blood cells in the right hind footpad after the dosing, and investigators reported a significant increase in DTH response (as measured by footpad thickness) relative to vehicle control in the middle dose group of the normal mice only.

Based on this observation, the authors concluded that stevioside was an immunomodulator of DTH. Thus, this study did not provide direct evidence for the allergenic potential of stevioside, but suggested that it may enhance the delayed hypersensitivity reaction of other allergens. Sehar et al. (2008) did not provide a description of the purity of the stevioside preparation used in their study design, nor was there a discussion of why the modulated DTH effect was not observed at the highest dose group, thereby limiting the certainty of the authors' conclusions. No confirmatory studies in the mouse or other animals have been conducted. Additionally, this novel finding has not been observed in humans to date, so if in fact purified steviol glycosides do modulate DTH reactions in mice, it is not clear that this effect is relevant in humans. It should also be pointed out that several animal toxicology studies – including dermal and ingestion exposure studies – have been conducted on various high purity steviol glycosides (individual compounds and mixtures) since 2008, none of which produced evidence for hypersensitivity or allergic potential (reviewed by EFSA, 2010; Health Canada, 2012).

3.3. Evidence for stevia allergenicity in the literature: reviews

In addition to the two case study reports and animal study, there were two reviews that address stevia products as potential allergens. At the time of its publication, an abstract for a review of stevioside safety by Geuns (2003) stated that no allergic reactions had been associated with stevioside use, although this issue is not actually addressed in the main text of the review. A more recent blinded review of stevia was conducted by a multidisciplinary group of researchers and clinicians and published by the Natural Standard Research Collaboration (Ulbricht et al., 2010). The group concluded that exposure to stevia or stevia products is “likely unsafe” for patients with known allergies to members of the Asteraceae family (Ulbricht et al., 2010). However, the authors stated that this is a theoretical precaution, and cite the 2003 Geuns review in noting that no allergic reactions have been reported in the literature.

3.4. Evidence for stevia allergenicity: consumer surveillance studies

Kingston et al. (2013) reported on a direct market-to-consumer surveillance program set up on behalf of a corporate client to monitor for spontaneously reported adverse health effects potentially associated with the Truvia® brand sweetener, a combination of erythritol (a compound known to have very low allergenic potential), flavors, and highly refined steviol glycosides or stevia leaf extract. The program was operated by a triple board licensed health-care practice and industry poison control center affiliated with the University of Minnesota, USA, and was conducted from 2008 to 2012. Evaluation of the incident data indicated that reports of any adverse clinical effects were rare, with all incidents (not just allergenic) occurring at a rate of 1.1 per 10 million servings sold. Incidents of gastrointestinal effects comprised nearly half of the complaints (0.48 incidents/10 millions servings), followed by incidents of the central nervous system (0.33 incidents/10 millions servings) and skin (0.28 incidents/10 millions servings) (Table 2).

Table 2

Results of 2008–2012 surveillance study of stevia-based product post-market customer health effects (data from Kingston et al., 2013).

Organ system	Adverse event prevalence per 10 ⁶ servings
Gastrointestinal	0.5
Hematological	0.01
Cardiovascular	0.04
Genitourinary	0.04
Respiratory	0.09
Dermatologic	0.3
Ocular	0.0
Central nervous system	0.3
Miscellaneous	0.0

The study monitors concluded that these rates were especially low in all categories, and supported the safety profile of steviol glycosides. There was no information provided on whether any of the adverse incidents reported were allergy-type events other than what might be postulated from reported clinical effects such as dermal or respiratory symptoms, and there was no further follow-up received from consumers or their healthcare providers to confirm such effects were specifically allergy related. While low levels of complaints were reported, however, they tended to be general complaints commonly observed in many epidemiological studies that would not be clearly or solely indicative of hypersensitivity (e.g., GI upset, headache). As noted above, this sweetener also contains erythritol, which has been implicated in some relatively rare cases of hypersensitivity reactions (Hino et al., 2000; Shimizu et al., 2012; Shirao et al., 2013; Sugiura et al., 2013; Yunginger et al., 2001). Hypothetically, if there had been any hypersensitivity cases associated with Truvia consumption, the evidence suggests that they would have more likely related to erythritol sensitivity than steviol glycosides. Overall, the surveillance results are in agreement with the fact that purified steviol glycoside products have not been featured on food allergen discussion boards or lists within high profile food allergy networks.

3.5. Evidence of potential stevia allergenicity in news reports

A more general search of news accounts of the potential stevia-allergy association also yielded very little, though a recent news report out of New Zealand highlights another potential incident of stevia hypersensitivity.⁵ In this case, a 15-year old female experienced bouts of nausea, vomiting, dizziness and fainting, which were later associated with her consumption of certain stevia flavored water products (e.g., “360”). Avoidance of these and all products containing stevia extracts resulted in a cessation of symptoms, suggesting that stevia was responsible. However, no oral challenge trial was conducted to prove the stevia allergenicity, and no skin prick tests were conducted to establish allergic sensitization to stevia in this patient. Also, it is unknown if this patient was sensitized to other *Asteraceae* plants or components. Furthermore, several ingredients can be added to flavored water and other drinks, so it is difficult to establish from anecdotal evidence that purified stevia extract is the allergenic culprit in this case as well as in other anecdotes. It is unfortunate that the apparently conclusive diagnosis of stevia allergy in this story was not supported by a more thorough investigation of all potential sources of allergens, a more complete patient history, and an appropriate challenge-avoidance testing that would

⁵ <http://www.3news.co.nz/Stevia-sweetener-blamed-for-illness/tabid/423/articleID/296436/Default.aspx>.

have been required if it had been reported in a peer-reviewed scientific journal.

3.6. Evidence for stevia plant constituent allergens

Although the hypersensitivity reactions associated with major food allergies are commonly initiated by specific proteins, there have been no such constituents reported in the specifications of highly purified formulations of steviol glycosides. However, it is entirely possible that proteins may be present at levels relevant for allergenicity in purified stevia products. It is also possible that there are other constituents of the *S. rebaudiana* plant that may be reasonable allergen candidates. The *Asteraceae* family includes approximately 20,000 species of plants, some wild and some widely cultivated. Allergens in *Asteraceae* species originate from three sources, proteins present mostly in pollen or food derived from the plants and sesquiterpene lactones (SLs) present in various parts of the plant (Lundh et al., 2006; Warshaw and Zug, 1996). *Asteraceae* pollen allergens may be plant-specific or pan-allergens, i.e., allergenic proteins found widely in plants (Asero et al., 2011; Egger et al., 2006). Several pollen allergens have been identified in various *Asteraceae* species including ragweed, mugwort, and sunflower (Egger et al., 2006). Pollen-food syndrome does occur between *Asteraceae* species and numerous foods not restricted to the *Asteraceae* family (Egger et al., 2006). Allergic reactions have been documented to several foods from the *Asteraceae* family, most notably sunflower seed (Besler et al., 2001). Although sunflower seed allergy is more common, other foods from the *Asteraceae* family, such as lettuce, chicory, artichoke, chamomile, and echinacea are rarely implicated in food allergies.

The *Asteraceae* pollen protein allergies manifest primarily as rhinoconjunctivitis from pollen allergy producers such as ragweed and are classic IgE-mediated hypersensitivity reactions. Sensitization to ingested allergens by prior exposure to related inhaled pollen allergens is a well-known phenomenon known as the oral-allergy syndromes or pollen-food syndromes (Asero et al., 2011; Bohle, 2007; Egger et al., 2006). *Asteraceae* pollen allergens are known to be associated with allergies to foods in other botanical families (Egger et al., 2006); however, foods of the *Asteraceae* family are not involved in most of these pollen-food syndromes. One allergen found in pollen, the lipid transfer protein (LTP), is a soluble protein also found in plant cell walls that can be present at relatively high levels (up to 4% of soluble protein) in plants (Kader, 1996). LTP has been identified as the cause of IgE-mediated anaphylaxis and hypersensitivity in two studies of lettuce allergy via ingestion (Bascones et al., 2009; San Miguel-Moncín et al., 2003). Another allergen that could be involved in pollen-food syndrome is the thaumatin-like protein (TLP), which has also been identified as an allergen in lettuce (Munoz-Garcia et al., 2013).

As noted above, the most commonly allergenic food in the *Asteraceae* family is sunflower seed (Besler et al., 2001). Two food allergens have been identified from sunflower seed – a 2S albumin (Kelly and Hefle, 2000) and LTP (Yagami, 2010). Allergies to the common salad ingredient lettuce are rare (Franck et al., 2000; Olive-Perez and Pineda, 2003; Vila et al., 1998). Previous sensitization to pollen carrying LTP via inhalation is likely required to initiate lettuce hypersensitivity. The same is true of TLP but it has not been as well documented. Chicory is less commonly used in foods, but chicory allergy has been described and is known to be cross-reactive with pollens; however, chicory allergens have not been identified (Helbling et al., 1997; Minciullo et al., 2004). Similarly, allergy to endive – a close relative to chicory – has been rarely described, and the endive allergens remain to be elucidated (Helbling et al., 1997). Artichoke is yet another member of the *Asteraceae* family with which an allergy is associated yet quite rarely described and for which the allergens are unknown (Gadban et al., 2003).

While contact allergy to chamomile tea has been frequently reported, IgE-mediated anaphylaxis is rare (Andres et al., 2009; Benner and Lee, 1973; Casterline, 1980; Reider et al., 2000; Sanchez Palacios et al., 2007; Subiza et al., 1989). Reider et al. (2000) reported that patients with positive IgE reactions to chamomile also reacted to related allergens including several inhalation allergens from the *Asteraceae* family such as mugwort. The actual allergenic proteins were not specifically identified, but appeared to be different from LTP based on a molecular weight analysis. Andres et al. (2009) confirmed allergy to German chamomile tea that was not related to the presence of SL. They also found cross-reactivity to mugwort pollen in patients with a history of chamomile hypersensitivity. Ingestion of Echinacea has also been reported to cause anaphylactic reactions, but no specific allergen has been identified (Huntley et al., 2005; Mullins, 1998; Mullins and Heddle, 2002; Myers and Wohlmuth, 1998).

Asteraceae plants are also known for causing contact allergy that has been attributed to the presence of SLs (Gordon, 1999; Jovanovic et al., 2004). These are delayed (Type IV) hypersensitivity reactions mediated by T-lymphocytes that are manifested primarily as eczema, urticaria and other forms of dermatitis. The allergenic SLs capable of producing these dermatitis responses can generally be narrowed down to six structural groups: eremophilanolides, germacranolides, eudesmanolides, guaianolides, pseudoguaianolides, and xanthanolides. Common to most allergenic SLs is an alpha-methylene moiety on the lactone ring that is thought to act as a hapten by reacting with protein amino acids, ultimately forming a complete antigen (Warshaw and Zug, 1996).

Several analytical studies have been published on the phytochemical components of the *S. rebaudiana* plant (reviewed in Wölwer-Rieck, 2012). While SLs are common to many plants in the *Asteraceae* family, and even some stevia plant species (de Heluani et al., 1989; Goyal et al., 2010), there is no evidence that SLs are present in *S. rebaudiana* leaf extracts. Smaller lactones have been reported to be present in *S. rebaudiana* leaves (Markovic et al., 2008), though these molecules lack the α -methylene moiety on the lactone ring associated with most allergenic SLs. A number of sesquiterpenes have been detected in *S. rebaudiana* leaf extracts, the most abundant of which include β -caryophyllene, caryophyllene oxide, and spathulenol (Cioni et al., 2006; Hossain et al., 2010; Markovic et al., 2008; Muanda et al., 2011). It has been reported that autooxidation products of fragrance terpenes (such as caryophyllene oxide) can be contact allergens (Matura et al., 2005; Sköld et al., 2006), and therefore this represents a potential *S. rebaudiana* plant allergen. However, even if certain individuals react to the caryophyllene oxide present in the essential oil of the *S. rebaudiana* plant, it is not likely that this component is present in the highly refined steviol glycoside products approved for use in the U.S. market, as caryophyllene oxide is soluble in alcohol (EFSA, 2009) and therefore would be removed during the alcohol extraction refinement process. Even so, it is only relevant to contact dermatitis and does not provide any evidence for adverse effects from exposure via the oral intake of steviol glycosides or stevia leaf extract meeting the JECFA specifications. As of yet, substantiated reports of contact dermatitis from consumers or producers of stevia have not been reported in the literature.

4. Conclusions

Theoretically, crude extracts of *S. rebaudiana* previously sold as dietary supplements have a higher allergenic potential than high purity stevia-based sweeteners because crude extracts have a higher likelihood of containing allergenic substances common to the *Asteraceae* family. As of this writing, there are very few studies published in the scientific literature that examine the allergenicity potential of steviol glycosides. Reports of stevia hypersensitivity, even

to crude extracts, are very rare and contain questionable substantiation in concluding that hypersensitivity to stevia occurred. During the regulatory reviews of high-purity steviol glycoside sweeteners, the potential for hypersensitivity was dismissed or minimized by every national and international food safety authority.

High purity steviol glycosides use is growing, but currently they are found in only a limited number of food products. Tabletop sweetener use is also growing, but total population exposure is still quite limited relative to other non-nutritive sweeteners. Thus, while there is no explicit evidence to support the claim that high purity steviol glycosides are allergenic, this may be a reflection of the low population-wide exposure (i.e., small opportunity for allergenic reactions to occur at detectable rates in the population), rather than proof that such products are not allergenic. A clearer picture of their allergenic potential will emerge as consumption of steviol glycoside sweeteners grows in the future.

In the absence of more robust studies on the issue, advice on popular Internet websites that high-purity stevia-based sweeteners may cause allergic reactions is likely to persist. Studies designed to examine steviol glycoside de novo sensitization or cross-reactivity would be beneficial for developing a more complete characterization of the allergenicity potential of high purity steviol glycoside sweeteners. Health-care providers should advise patients with *Asteraceae* plant allergies that the potential for cross-reactions to stevia-based sweeteners is low based on currently available information, but that such reactions cannot be completely ruled out without further clinical research.

Conflict of interest

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Transparency document

The [Transparency document](#) associated with this article can be found in the online version.

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