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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.

Contents

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; SCI, 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 ≥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 (Joint FAO/WHO Expert Committee on Food Additives (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 (Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2008). Similar assessments and conclusions on safety have been conducted by the European Food Safety Agency (European Food Safety Authority (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 (≥95%) meet the US Food and Drug Administration standard for being classified "Generally Recognized as Safe" (GRAS) (United States Food and Drug Administration (USFDA), 2014).

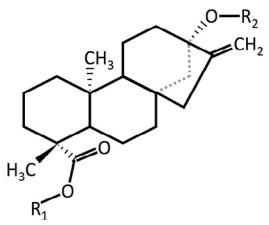

Fig. 1. Steviol glycoside – aglycone structural core.

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

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→1)	150–250	Yes
Rebaudioside A	β-Glc	β-Glc-β-Glc(2→1) ∠ β-Glc(3→1)	200–300	Yes
Rebaudioside B	H	β-Glc-β-Glc(2→1) ∠ β-Glc(3→1)	150	–
Rebaudioside C	β-Glc	β-Glc-α-Rha (2→1) ∠ β-Glc(3→1)	30	–
Rebaudioside D	β-Glc-β-Glc(2→1)	β-Glc-β-Glc(2→1) ∠ β-Glc(3→1)	221	Yes
Rebaudioside E	β-Glc-β-Glc(2→1)	β-Glc-β-Glc(2→1)	174	–
Rebaudioside F	β-Glc	β-Glc-β-Xyl(2→1) ∠ β-Glc(3→1)	200	–
Rebaudioside X	β-Glc-β-Glc(2→1) ∠ β-Glc(3→1)	β-Glc-β-Glc(2→1) ∠ β-Glc(3→1)	200–350[b]	Yes
Dulcoside A	β-Glc	β-Glc-α-Rha(2→1)	30	–
Rubusoside	β-Glc	β-Glc	114	–
Steviolbioside	H	β-Glc-β-Glc(2→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 FDA GRAS Notice No. GRN 473 (FDA, 2013).

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