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# Hypersensitivity reactions associated with nutraceuticals and dietary supplements: A narrative review

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## Abstract

The global use of nutraceuticals and dietary supplements—including vitamins, minerals, probiotics, and botanical extracts—has increased substantially, driven largely by consumer perceptions of safety and health benefits. However, their potential to cause hypersensitivity reactions (HSRs) is underrecognized. This review synthesizes published case reports, case series, systematic reviews, and pharmacovigilance data to characterize HSRs linked to these products, identify risk factors, and examine diagnostic and regulatory challenges. We classified reactions as immediate (< 1-6 h after administration), non-immediate (> 1-6 h after administration to several weeks). Immediate HSRs, including anaphylaxis, have been reported after vitamins B complex, short-chain galacto-oligosaccharides (GOS), whole-food supplements such as spirulina, natto (poly[γ-glutamic acid]) and royal jelly, and botanical/plant derived products; diagnosis commonly used skin-prick and intradermal testing and basophil activation tests. Non-immediate HSRs—ranging from maculopapular eruptions to severe cutaneous adverse reactions—have been associated with cobalamin, chromium picolinate, alpha-lipoic acid, diindolylmethane (DIM), glucosamine/chondroitin, and euglena; diagnosis often relies on patch testing, lymphocyte transformation assays, and cautious drug provocation when indicated. These products can also cause allergic contact dermatitis, and occupational sensitization (e.g., rhinitis/asthma) has been reported in workers exposed to psyllium and Aspergillus oryzae–derived lactase. Diagnostic accuracy is limited by nonstandardized reagents, variable test concentrations, complex product formulations, and cross-reactivity (notably within botanical families such as Asteraceae and among plant proteins/legumes), complicating interpretation and increasing risk for atopic individuals. Evidence remains dominated by case-based reports and passive surveillance. To reduce risk, we recommend heightened clinician awareness, development of standardized diagnostic reagents and protocols, mandatory adverse-event reporting, clearer ingredient labeling, and premarket allergenicity assessment.

**Key words:** Anaphylaxis, Dietary supplements, Hypersensitivity reactions, Nutraceuticals, Vitamins

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**Abbreviations:**

| | |
|---|---|
| ACD | allergic contact dermatitis |
| AGEP | acute generalized exanthematous pustulosis |
| BAT | basophil activation test |
| DPT | drug provocation test |
| DRESS | drug reaction with eosinophilia and systemic symptoms |
| HSR | hypersensitivity reaction |
| IDT | intradermal test |
| IHR | immediate hypersensitivity reaction |
| LTT | Lymphocyte Transformation Test |
| NIHR | non immediate hypersensitivity reaction |
| PTP | prick to prick |
| SCAR | severe cutaneous adverse drug reactions |
| sIgE | specific IgE |
| SJS/TEN | Stevens-Johnson-Syndrome/Toxic Epidermal Necrolysis |
| SPT | skin prick tests |

## Introduction

The use of dietary supplements has been steadily increasing worldwide. A key factor driving this growth is consumer confidence in these products, based on the belief that they are natural, safe, and capable of promoting health.[1] However, despite the widespread acceptance of nutraceuticals and dietary supplements, there has been a rising number of reports concerning adverse effects and allergic reactions associated with their consumption. Most of these reports take the form of case series or individual case reports, with hypersensitivity reactions (HSR) ranging from mild symptoms such as rashes and hives to severe reactions that affect multiple body systems, potentially leading to life-threatening anaphylaxis and severe cutaneous adverse drug reactions (SCARs).[2]

The complexity of the components found in nutraceuticals and dietary supplements, along with the diversity of manufacturing processes and varying quality control standards, make risk assessment and allergen identification in these products challenging.[3] Additionally, the lack of comprehensive data and accurate communication about potential risks may leave consumers unaware of the hidden dangers associated with these products.[4-5]

Therefore, this narrative review will comprehensively evaluate existing academic data regarding HSRs related to nutraceuticals and dietary supplements. It aims to enhance our understanding of the prevalence and classification of HSRs, associated risk factors, and appropriate management and prevention strategies related to these products. This information will provide valuable insights for consumers, medical professionals, and regulatory agencies, promoting the safe and effective use of health products based on empirical evidence and supporting the development of future policies regarding their safe and effective use.

## Nutraceuticals and dietary supplements

Nutraceuticals and dietary supplements have grown in popularity worldwide as alternative health solutions aimed at promoting well-being and preventing chronic disease. Nutraceuticals—products derived from food sources that provide benefits beyond basic nutrition—include vitamins, minerals, herbs, amino acids, and fatty acids. Dietary supplements are intended to supplement the diet and commonly include probiotics, fish oils, and herbal extracts.[1]

Regulation of nutraceuticals and dietary supplements varies between countries. These products are generally classified differently from conventional pharmaceuticals, and many supplements can be sold without a prescription. Although, manufacturers must comply with safety and labeling requirements, the regulatory framework often permits market entry without extensive premarket clinical testing. Consequently, a wide range of products may reach consumers despite variable quality control and limited clinical evaluation.[3]

Despite widespread use and a public perception of safety, nutraceuticals and dietary supplements can cause adverse effects, including HSRs. These range from mild allergic symptoms to severe, life-threatening reactions and pose significant health risks.[2] As global use increases, it is crucial to better characterize the clinical presentations and identify the agents implicated in HSRs related to these products.

## Adverse drug reactions

Adverse Drug Reactions (ADRs) are classified based on the World Health Organization (WHO) into predictable reactions (Type A) and unpredictable reactions (Type B), which include HSRs.[6] Although dietary supplements and nutraceuticals do not fall under the strict definition of "drugs," this classification will be applied to evaluate the risks and patterns of reactions associated with these products in this review.[2]

## Hypersensitivity reactions (HSRs) to drugs

HSR to drugs are classified by clinical features, and timing after exposure into two main categories. Immediate hypersensitivity reactions (IHRs) occur within 1–6 hours of drug administration and are typically IgE-mediated (Type I), presenting most commonly with cutaneous features such as urticaria and angioedema; severe cases (anaphylaxis) may involve respiratory, or circulatory compromise. Non-immediate hypersensitivity reactions (NIHRs) arise more than 6 hours after exposure and can appear days to weeks later, ranging from delayed urticaria and maculopapular eruptions to SCARs such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).

Mixed or overlapping phenotypes can occur in complex clinical scenarios and may not be fully captured by a strict time-based cutoff. In addition to classic IHRs (within 1–6 hours) and delayed reactions (>6 hours to weeks), an accelerated non-immediate pattern (≈1–24 hours) is recognized. These accelerated reactions often involve T-cell–mediated mechanisms but may also include mast-cell activation, producing clinical features of both immediate and delayed responses.[6]

Diagnosis begins with a thorough history and physical examination but is often challenging when patients receive multiple products or when infectious or other causes mimic HSRs. Further testing such as skin tests (ST), including skin prick test (SPT), prick to prick test (PTP), intradermal test (IDT), and patch test, *in vitro* assays, and, when safe, drug provocation tests (DPT) are frequently required to confirm the diagnosis and identify safe alternatives (**Figure 1**).[7-10] Accurate diagnosis is essential: overdiagnosis may lead to unnecessary avoidance of effective drugs, while underdiagnosis can expose patients to life-threatening risk allergen re-exposure.

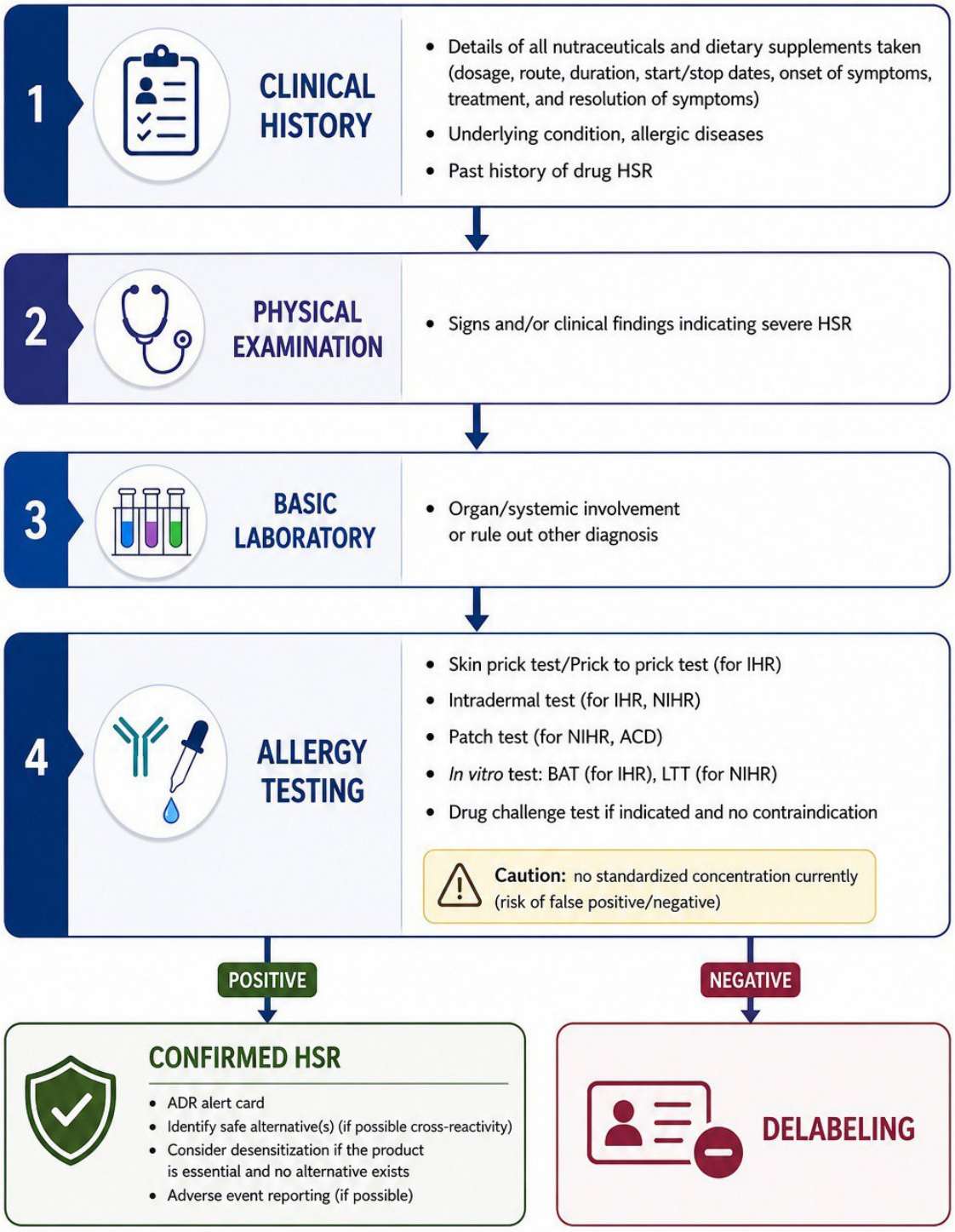


**Figure 1. Diagnostic algorithm for suspected hypersensitivity reactions to nutraceuticals and dietary supplements.**

**Abbreviation:** ACD, allergic contact dermatitis; ADR, adverse drug reaction; BAT, basophil activation test; HSR, hypersensitivity reactions; IHR, immediate hypersensitivity reaction, NIHR, non-immediate hypersensitivity reaction; LTT, lymphocyte transformation test

## Search strategy (narrative review)

We performed a narrative review using a structured search primarily in PubMed/MEDLINE. Reference lists of retrieved articles and Google Scholar were hand-searched to identify additional relevant reports. Because primary studies on this topic are scarce, we included case series and case reports with physician-documented HSRs and/or additional drug-allergy investigations (skin tests, *in-vitro* assays, and/or drug provocation tests). We excluded reports that lacked clear documentation of an HSR or described ADRs not consistent with HSR.

## Results

### 1. *Immediate Hypersensitivity Reaction associated with Nutraceuticals and dietary supplements*

IHRs can manifest clinically as conditions ranging from urticaria and angioedema to severe anaphylaxis. **Table 1** provides a summary of these reported IHRs associated with nutraceuticals and dietary supplements, outlining the identified culprit agents and diagnostic methods.

**Table 1. Summary of Documented Immediate Hypersensitivity Events Associated with Nutraceuticals and Dietary Supplements.**

| Nutraceutical / Dietary Supplement | Clinical presentation | Allergens / Cross reactivity | Confirmation methods / Tests (reported concentrations) | References |
|---|---|---|---|---|
| Thiamine (vit B1) | Urticaria, anaphylaxis | Thiamine formulations | SPT 1 mg/mL; IDT 0.5–1 mg/mL; histamine release assay; specific IgE (ELISA) | [11-20] |
| Riboflavin (vit B2) | Anaphylaxis (energy drinks, supplements) | Riboflavin formulations | SPT 0.1 & 1 mg/mL; IDT 0.001–1 mg/mL | [21-22] |
| Dexpanthenol (vit B5) | Anaphylaxis | Dexpanthenol in multivitamin tablets | Scratch tests | [23] |
| Folic acid (vit B9) | Urticaria, anaphylaxis | Possible cross reactivity with methotrexate (in vitro) | SPT up to 5 mg/mL; IDT range 0.00005–10 mg/mL; histamine release assays; ELISA/dot immunoblot | [24-33] |
| Cobalamin (vit B12) | Immediate urticaria / anaphylaxis (often after IM/SC) | Hydroxycobalamin or cyanocobalamin; PEG excipient in some cases | SPT 1 mg/mL; IDT 0.1 & 0.01 mg/mL; DPT (when indicated); acute tryptase measurement | [34-43] |
| Vitamin D3 | Anaphylaxis | N/A | Naranjo scoring system | [45] |
| Galacto oligosaccharides (GOS, prebiotic) | Anaphylaxis | Specific GOS fractions (short chain) | SPT 7.2 & 14.4 mg/mL; BAT (high sensitivity/specificity); DPT (when indicated) | [46-47] |
| Probiotic | Anaphylaxis | Possible contamination of probiotic preparations with milk/egg allergens | N/A | [48-50] |
| Alpha lipoic acid | Angioedema, anaphylaxis (often within first week) | N/A | Spontaneous adverse-event reports; causality assessment (WHO-UMC) | [51] |
| Natto (fermented soybean) | Anaphylaxis | poly(γ-glutamic acid) (PGA) from natto mucilage; linked to soy allergy; possible sensitization via dermal/ environmental exposure | PTP to natto mucilage, SPT to PGA (1mg/ml) | [52] |
| Royal jelly | Anaphylaxis | Royal jelly protein | PTP/sIgE (inhouse radioallergosorbent test) | [53] |
| Spirulina (Arthrospira platensis) | Anaphylaxis | Spirulina platensis proteins | SPT to diluted spirulina and S. platensis (example: 0.03 mg/mL reported) | [54] |
| Chamomile | Anaphylaxis, acute rhinitis, and contact urticaria, | Asteraceae family cross-reactivity (e.g., mugwort) | SPT/sIgE, provocation test, (SDS-PAGE) and immunoblots | [55] |
| Echinacea | Anaphylaxis, acute asthma, generalized urticaria/ angioedema | Cross-reactivity with other Asteraceae species (ragweed, mugwort, chrysanthemums, sunflowers) | SPT and radioallergosorbent testing to echinacea extracts | [56] |
| Flaxseed (Linum usitatissimum) | Anaphylaxis, angioedema, urticaria | seed storage proteins (2S albumin, 11S globulin), possible MDH-1; cross-reactivity with peanut, soybean, rapeseed, lupine, wheat, tree nuts, rape pollen | PTP/SPT with heated flaxseed flour extract (e.g., 0.1 mg/mL); IDT diluted 1:10 (0.01 mg/mL); SDS-PAGE and IgE immunoblotting to identify IgE-binding proteins | [57-67] |

**Abbreviation:** BAT, basophil activation test; ELISA, Enzyme-linked Immunosorbent Assay; IDT, intradermal test; MDH, malate dehydrogenase; PGA, poly (γ-glutamic acid); PTP, prick to prick test; SDS-PAGE, Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis; SPT, skin prick test; sIgE, specific Immunoglobulin E

### 1.1 Vitamins and Minerals

IHRs to vitamins is most commonly reported for thiamine, folate, and cobalamin, with fewer reports for riboflavin, dexpanthenol, and vitamin D. Diagnostic confirmation has relied on positive skin tests, specific IgE or mediator-release assays (tryptase, histamine), and, when safe, DPT. Excipients (e.g., PEG) have been implicated in some cases—particularly with cobalamin—and parenteral administration (IM/SC/IV) appears to carry higher risk than oral dosing. Clinically, evaluation should prioritize assessment of both the vitamin and any excipients and the route of exposure, use validated tests when available, and reserve controlled DPT as the diagnostic gold standard.

#### *1.1.1 Vitamin B1 (thiamine) (case reports)[11-20]*

Although IHRs to oral thiamine are uncommon, several cases of generalized urticaria and anaphylaxis —including shock—have been reported following intravenous thiamine. The mechanism is unclear but may involve phosphorylation of thiamine hydrochloride at the intestinal mucosa. Diagnostic confirmation has used SPT with a 1 mg/ml thiamine solution[11,14] and IDT at 0.5 mg/ml or 1 mg/ml solution.[11-12] Additionally, histamine release assays,[14] along with specific IgE testing by ELISA,[12,20] have also been employed to support the diagnosis.

#### *1.1.2 Vitamin B2 (riboflavin) (case reports)[21-22]*

Anaphylaxis to riboflavin has been reported after ingestion of energy drinks, soft drinks, and multivitamin tablets. Diagnostic confirmation has used SPT with riboflavin 5' sodium phosphate at 0.1 and 1 mg/mL, and IDT accross 0.001-1 mg/ml; these concentrations were validated in a control group of 10 tolerant subjects.[21] In another report, riboflavin sodium phosphate and riboflavin tetrabutyrate produced positive IDT results at 0.001 mg/ml.[22]

#### *1.1.3 Vitamin B5 (dexpanthenol) (case report)[23]*

A case of anaphylaxis was reported after ingestion of a multivitamin tablet containing vitamins B1, B2, B6, B12, folic acid, and dexpanthenol, along with excipients such as cellulose, lactose, calcium stearate, silicon dioxide, and glycerin. Scratch testing with the multivitamin tablet provoked throat tightness, facial edema, and breathlessness within 15 minutes. After treatment, subsequent targeted scratch tests under emergency conditions were negative for the individual vitamins (B1, B2, B6, B12, and folic acid).

#### *1.1.4 Vitamin B9 (folic acid) (case reports/case series)[24-33]*

IHRs to folic acid—ranging from urticaria to anaphylaxis—have been reported, with some cases confirmed by DPT. These reactions have been associated with folic acid itself or with multivitamin tablets and other supplements. SPT at a maximum concentration of 5 mg/ml demonstrated positivity in allergic subjects but were negative in healthy controls.[30,33] IDT concentrations have varied widely (0.00005, 0.005, 0.1, and 10 mg/ml). Additional tests, such as histamine release assays with folic acid at concentrations of 0.01 and 0.001 mg/mL,[33] as well as dot immunoblot assay or an ELISA for IgE antibody to folate-human serum albumin,[30] have shown positive reactions in allergic individuals compared to normal healthy controls. Furthermore, *in vitro* cross-reactivity with methotrexate was demonstrated using the histamine release test.[33]

#### *1.1.5 Vitamin B12 (cobalamin) (case series)[34] (case reports)[35-43]*

The largest series on Vitamin B12 hypersensitivity, reported by El Rhermoul FZ et al.,[34] found that 62% (18/29) of patients experienced immediate reactions, of whom 44% (8/18) having anaphylaxis attributed equally to hydroxycobalamin and cyanocobalamin; most events were classified as severe (grade 3). Diagnosis relied mainly on SPT (1 mg/ml) and IDT (0.1 and 0.01 mg/ml), with DPT performed when skin tests were negative. Among immediate reactors, positive tests occurred in 38% by SPT alone, 38% by IDT alone, and 25% by both; acute tryptase was markedly elevated in all five patients where available measurements. In one patient with an IHR, SPT identified polyethylene glycol (PEG) excipient allergy rather than direct cobalamin sensitivity. Other reports describe immediate urticaria or anaphylaxis after Vitamin B12 injection,[35-39,44] some managed successfully by desensitization.[38,41,43] Overall, available data suggest cobalamin hypersensitivity is more likely following intramuscular or subcutaneous administration than oral forms. Reported cases indicate that patients can be allergic to either hydroxycobalamin or cyanocobalamin, often tolerating the other form. Additionally, allergies to both compounds have also been documented.[34,40,42]

#### *1.1.6 Vitamin D (case report)*

Ridge A et al.[45] reported a case of a 53-year-old female with asthma and irritable bowel syndrome who experienced suspected mixed IHR and NIHR to weekly oral vitamin D (350 mcg cholecalciferol). Her immediate reactions included rapid-onset gastrointestinal symptoms such as dyspepsia and cramps, followed by a pruritic vesicular rash and asthma exacerbation. Although total immunoglobulin E levels were elevated, SPTs for vitamin D and common allergens, as well as patch tests, were negative. The Naranjo scoring system classified her reaction as a 'probable' drug allergy with a score of 7. After undergoing desensitization, the patient successfully tolerated a daily dose of 1000 IU of vitamin D.

### 1.2 Prebiotics/Probiotics

*1.2.1 Prebiotics: Galacto-oligosaccharides (GOS) (case series)*

Soh JY, et al.[46] investigated anaphylaxis to galacto-oligosaccharides (GOS) in an atopic Singaporean population. Of 13 subjects orally challenged with Vivinal™ GOS (vGOS), six experienced IHRs within 15-70 minutes, including four cases of anaphylaxis characterized by symptoms like sneezing, urticaria, and laryngeal tightness. Diagnosis involved SPT (7.2 and 14.4 mg/ml) and BAT to GOS, with BAT showing high sensitivity and specificity. The authors estimated vGOS allergy prevalence at up to 3.5% in this atopic group and demonstrates that a modified GOS formulation (Oligomate) was tolerated, underscoring the importance of GOS structural variations in allergic potential and the utility of diagnostic testing for targeted advice. Another study described five cases of acute anaphylactic reactions triggered by short-chain galacto-oligosaccharides (scGOS) in cow's milk formula. All patients demonstrated IgE sensitization via SPTs and BATs to scGOS and its fractions containing three or more sugar units, but not to cow's milk or long-chain fructo-oligosaccharides (FOS).[47]

*1.2.2 Probiotic*

Probiotic compounds can contain hidden food allergens, such as cow's milk and egg, posing a risk to allergic individuals.[48] Contamination of probiotic preparations with milk allergens has been linked to anaphylaxis,[49] and instances of cross-sensitization with certain probiotics have also been observed.[50] Therefore, extreme caution is necessary when considering probiotic use in patients with cow's milk or hen's egg allergy.

### 1.3 Specific Bioactive Compounds

*1.3.1 Alpha-lipoic acid (spontaneous reporting systems)*

Alpha-lipoic acid is a naturally occurring mitochondrial cofactor and antioxidant found in small amounts in food and produced endogenously; it is also available as an oral supplement. It is generally well tolerated, with common adverse effects including mild gastrointestinal upset and headache. However, Gatti M, et al.[51] analyzed spontaneous reports and found that alpha-lipoic acid-containing dietary supplements can cause IHRs, including angioedema and anaphylactic shock. Many serious reactions occurred rapidly, often within the first week of alpha-lipoic acid administration. Causality assessments using the WHO-UMC system frequently indicated a probable association.

### 1.4 Fermented foods

*1.4.1 Natto (fermented soybean) (case report)*

Natto is a traditional Japanese food of fermented soybeans and should be avoided by individuals with soy allergies. Shigeno A, et al.[52] reported a case of a 49-year-old male who experienced immediate anaphylaxis while surfing, presenting with erythema, pruritus, and bradycardia. He had consumed natto 12 hours earlier; testing identified poly (γ-glutamic acid) (PGA) from natto mucilage as the allergen (positive PTP to natto mucilage and positive SPT to PGA at 1 mg/mL). The authors hypothesize that prior dermal exposure to PGA from jellyfish stings led to sensitization, illustrating how environmental exposures can trigger food allergies.

### 1.5 Animal-Derived Products

*1.5.1 Royal jelly (case report)*

Royal jelly is a nutrient-rich secretion produced by worker honeybees (Apis mellifera) that is used to feed larvae and the queen. It is available fresh, as freeze-dried powder, in capsules, or in combination supplements. Although allergic reactions are uncommon, Testi S, et al.[53] reported a case of severe anaphylaxis in a 28-year-old man with asthma. He developed dyspnea, wheezing, cough, chest tightness, and loss of consciousness; the reaction was initially suspected to be due to the antibiotic cefonicid. Further investigation showed he had ingested royal jelly after each cefonicid injection. Diagnostic testing identified royal jelly as the major allergen: a puncture test produced a 10 mm wheal, and an in-house radioallergosorbent test showed specific IgE binding to royal jelly (6.73%). SPT and IDT to cefonicid and penicillin derivatives were negative, and a supervised cefonicid injection produced no reaction.

### 1.6 Microalgae

*1.6.1 Spirulina (Arthrospira platensis) (case report)*

Spirulina is a blue-green microalga (cyanobacterium) commonly sold as a dried powder or in tablets. It is generally well tolerated at typical supplemental doses; however, allergic reactions can occur. One case report describes a 17-year-old male with atopic background who developed immediate anaphylaxis within ten minutes of ingesting a spirulina tablet. He experienced lip tingling, facial angioedema, generalized urticaria, gastrointestinal distress, wheezing, and inspiratory stridor. SPT was positive to diluted spirulina and specifically to Spirulina platensis at 0.03 mg/mL, identifying S. platensis as the causative allergen while other tablet ingredients tested negative.[54]

### *1.7 Botanicals/Plant-Derived Products*

Botanical reactions are often IgE-mediated and show clinically relevant cross-reactivity with related botanicals or pollens. Prior sensitizing exposures, atopy, and coexisting allergic disease increase risk (e.g., Asteraceae pollen cross-reacting with chamomile/echinacea). Storage proteins (11S globulins, 2S albumins) can mediate cross-reactivity between flaxseed and seeds/treenuts (**Figure 2**). Clinically, careful assessment of formulation and route, consideration of cross-reactivity, standardized testing when available, and controlled provocation testing in specialist settings are essential.

#### *1.7.1 Chamomile (case reports)*

Chamomile is a flowering plant in the Asteraceae family. Common preparations include dried-flower tea, aqueous or alcoholic extracts, essential oil, and topical formulations, which are used for their anti-inflammatory and antioxidant effects. A systematic review by Ostovar M et al.[55] on the adverse events associated with chamomile indicates that while clinical trials generally support its safety for controlled dosages, with only minor and self-limiting gastrointestinal issues and drowsiness reported, there are rare cases of severe IHRs. These reactions, which include anaphylaxis, acute rhinitis, and contact urticaria, often require clinical observation and treatment. Notably, in two cases of anaphylaxis, cross-reactivity to mugwort pollen was identified.

#### *1.7.2 Echinacea (case series)*

Echinacea, a flowering member of the Asteraceae family (also known as the coneflower family) that includes relatives such as ragweed, mugwort, chrysanthemums, and sunflowers, is widely used as an alternative medicine. However, HSRs such as acute asthma, generalized urticaria/angioedema, and severe anaphylaxis can occur, as reported by Mullins RJ et al.[56] Diagnosis relies on SPT and radioallergosorbent tests to echinacea extracts; SPTs showed positivity in affected patients and even in some atopic controls without prior exposure. Echinacea can cause cross-reactivity with other Asteraceae family plants, serving as a sensitization mechanism. This highlights atopic individuals' particular vulnerability to echinacea hypersensitivity, necessitating cautious use and comprehensive allergenicity assessment for this widely consumed supplement.

#### *1.7.3 Flaxseed (case reports)*[57-67]

Flax (Linum usitatissimum), also known as linseed, has gained popularity as a rich source of alpha-linolenic acid, a precursor of omega-3 fatty acids, and is associated with anti-inflammatory and antioxidant effects. However, several case reports, primarily in adults, describe immediate anaphylactic reactions to flaxseed. Diagnostic evaluation commonly involves PTP or SPT using heated flaxseed flour extract at 0.1 mg/mL, and IDT with a 1:10 dilution (0.01 mg/mL).[58,63] A large prospective study of 1317 allergy clinic patients found 77 (5.8%) were sensitized to flaxseed via PTP, with 73 having a history of atopy.

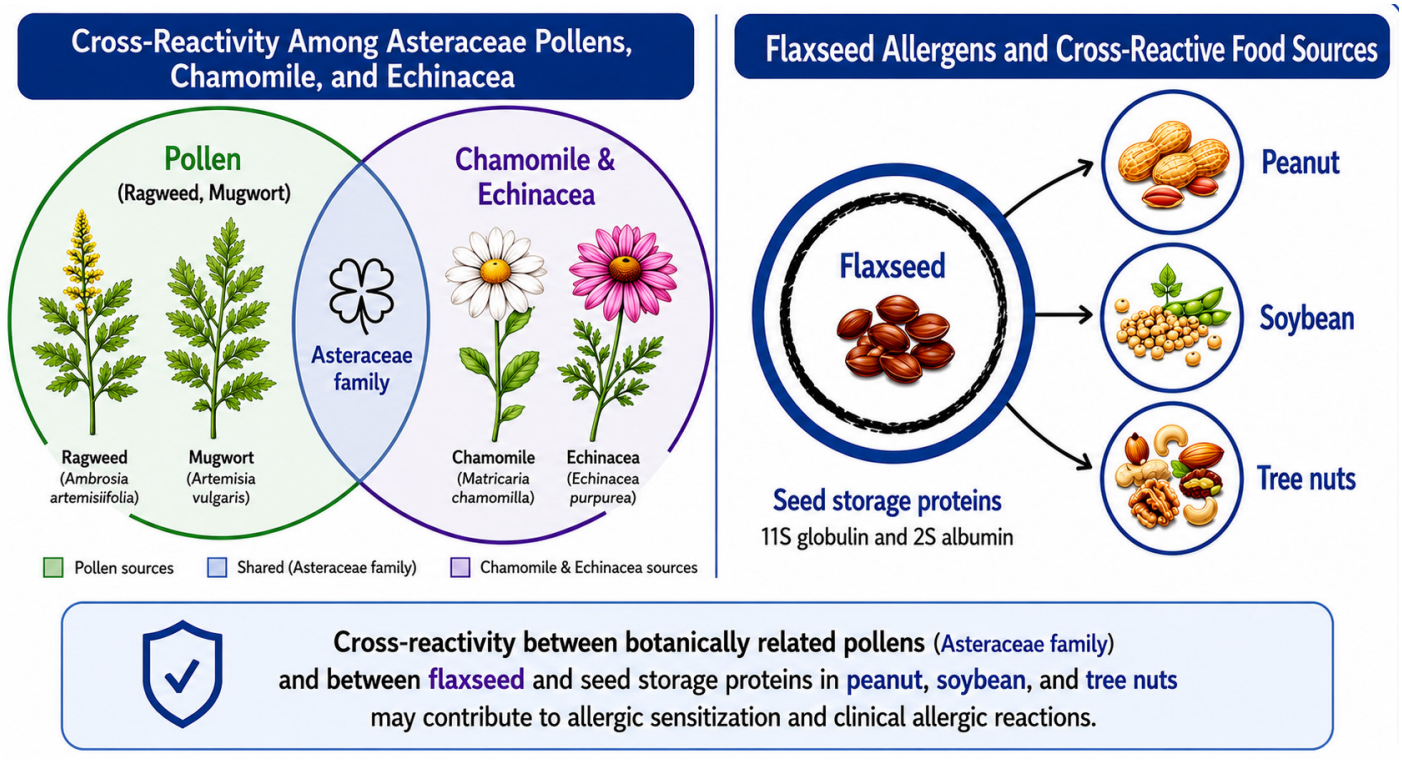


**Figure 2. Cross-reactivity within botanical families associated with hypersensitivity reactions to nutraceuticals and dietary supplements.**

Among these sensitized individuals, two experienced HSRs, one developing anaphylaxis and another angioedema.[61] Cross-reactivity has also been observed with other seeds (peanut, soybean, rapeseed, lupine), wheat and treenuts though its clinical relevance requires further challenge testing.[61,67-68] SDS-PAGE with IgE immunoblotting identified multiple IgE-binding proteins, notably at 20, 22, 25, 30, 35, 38, 43, and 53 kilodaltons.[57-58,62] Malate dehydrogenase (MDH-1), a 56 kDa dimer, has been suggested as a major allergen,[59,68] Later studies suggest that Storage proteins, such as the 11S globulin and the 2S albumin, are responsible for most cases of flaxseed allergy.[64-66]

## 2. *Non-Immediate Hypersensitivity Reaction associated with Nutraceuticals and dietary supplements*

NIHRs manifest across a wide clinical spectrum, from mild cutaneous reactions like delayed urticaria or maculopapular erythema to SCARs, which can be potentially fatal. **Table 2** summarizes reported NIHRs associated with nutraceuticals and dietary supplements, outlining the identified culprit agents and diagnostic methods.

### *2.1 Vitamins and Minerals*

#### *2.1.1 Vitamin B12 (cobalamin) (case series)[34]*

This case series on Vitamin B12 hypersensitivity, reported by El Rhermoul FZ et al.,[34] identified NIHRs to Vitamin B12 in 8 out of 29 patients (28%). Clinical presentations included maculopapular exanthems, angioedema, and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE). Diagnostic methods for these NIHRs primarily involved SPT and IDT, which were typically negative, followed by DPT. The major allergens were identified as hydroxycobalamin or cyanocobalamin, with a separate group presenting contact allergy to cobalt. Clinically, DPT proved effective in enabling patients to tolerate the index drug or an alternative Vitamin B12 formulation, facilitating continued treatment.

#### *2.1.2 Chromium picolinate (case report)*

Young PC et al.[69] reported a case of AGEP in a 32-year-old male, presenting with a sudden, extensive erythematous and pustular eruption on his trunk and extremities, accompanied by low-grade fever and malaise. The eruption appeared four days after he began daily intake of chromium picolinate as part of his exercise regimen, intended to strengthen muscle power. Despite negative patch tests for chromium picolinate and potassium dichromate, the diagnosis was established by the strong clinical correlation between symptom onset and supplement intake, complete resolution upon discontinuation, and successful treatment with oral prednisolone, all supported by histological findings characteristic of AGEP.

**Table 2. Summary of Documented Non-immediate Hypersensitivity Events Associated with Nutraceuticals and Dietary Supplements.**

| Nutraceutical / Dietary Supplement | Clinical presentation | Allergens / Cross reactivity | Confirmation methods / Tests (reported concentrations) | References |
|---|---|---|---|---|
| Cobalamin (vit B12) | Maculopapular exanthem, SDRIFE, angioedema (delayed) | Hydroxycobalamin or cyanocobalamin; contact allergy to cobalt reported | SPT/IDT often negative for delayed forms; DPT used for confirmation | [34] |
| Chromium picolinate | Acute generalized exanthematous pustulosis (AGEP) | Chromium compound | Patch testing may be negative; diagnosis by clinical timing, histology, resolution on withdrawal | [69] |
| Alpha lipoic acid | Delayed pruritic maculopapular rash | Alpha lipoic acid (supplement ingredient) | Patch test positive to Alpha lipoic acid and Alpha lipoic acid containing product (reported positive at 0.025% petrolatum) | [70] |
| Diindolylmethane (DIM) | DRESS (extensive eruption, eosinophilia, organ involvement) | DIM complex | Positive patch test to DIM complex; clinical/lab criteria for DRESS | [71] |
| Glucosamine / Chondroitin sulfate | Delayed hepatotoxicity ± rash, eosinophilia; possible DRESS | Glucosamine / chondroitin formulations | Clinical correlation, lab monitoring (liver function tests, eosinophils); skin tests usually not diagnostic | [72-75] |
| Euglena containing product | Erythema multiforme–type | Complex natural ingredients (Euglena, others) | Lymphocyte transformation test (LTT) reported positive but may be false positive; patch tests negative | [76] |

**Abbreviation:** Diindolylmethane, DIM; DPT, drug provocation test; DRESS, drug reaction with eosinophilia and systemic symptoms; IDT, intradermal test; LTT, Lymphocyte transformation test; SDRIFE, Symmetrical Drug-Related Intertriginous and Flexural Exanthema; SPT, skin prick test

### 2.2 Specific Bioactive Compounds

Most reactions to bioactive compounds are NIHRs (days to weeks after exposure), such as maculopapular exanthema with alpha-lipoic acid and DRESS with DIM and glucosamine/chondroitin; glucosamine/chondroitin have also been linked to idiosyncratic hepatotoxicity. IHRs (angioedema, anaphylaxis) are less common but have been reported. Early recognition and diagnosis are crucial to permit prompt discontinuation of the offending agent. Diagnostic evaluation of NIHRs relies primarily on patch testing and a high index of clinical suspicion; when available, the lymphocyte transformation test (LTT) may also be considered.

#### *2.2.1 Alpha-lipoic acid (case report)*

Rizzi A, et al.[70] reports a case of a 34-year-old woman who developed a non-immediate, pruritic maculopapular rash on her face and scalp after 10 days of taking a dietary supplement containing alpha-lipoic acid, along with other vitamins and ingredients. Diagnostic testing, four months later, included SPTs to all suspected drugs and the supplement, which were negative, but revealed an intense positive patch test reaction to the alpha-lipoic acid-containing supplement and alpha-lipoic acid itself. Alpha-lipoic acid, was identified as the major allergen, showing strong positive patch test reactions even at very low concentrations (0.025% in petrolatum), with healthy controls testing negative. Treatment involved discontinuing the supplement, which led to prompt resolution of symptoms.

#### *2.2.2 Diindolylmethane (DIM) (case report)*

A 36-year-old female, reported by Le TM, et al.,[71] developed DRESS, characterized by extensive painful erythema with pustules, facial and limb edema, eosinophilia, atypical lymphocytes, and liver involvement. The eruption appeared four weeks after she began daily intake of a DIM complex supplement. Diagnosis was confirmed through positive drug patch tests with the DIM complex. Treatment involved immediate discontinuation of the culprit supplement, oral prednisone (70 mg/day tapered over 8 days), and topical antibiotics and corticosteroids to manage skin manifestations.

#### *2.2.3 Glucosamine/chondroitin sulfate (case report),[72] (case series)[73-75]*

Glucosamine and chondroitin sulfate are thought to support cartilage growth and repair. Rare cases of drug-induced hepatotoxicity have been reported several weeks after starting these supplements, sometimes accompanied by rash, pruritus, and eosinophilia—findings suggestive of immune-mediated hypersensitivity.[72-75] Thus, beyond non-immunologic hepatotoxic mechanisms, these agents can potentially trigger HSRs, including severe presentations such as DRESS.

### 2.3 Microalgae

#### *2.3.1 Euglena-containing product (case report)*

A case report by Utsunomiya N, et al.[76] describes a 77-year-old male who developed an erythema multiforme-type eruption 10 days after ingesting a Euglena-containing product. The reaction was characterized by widespread red papules, edematous erythema, and erythroderma-like lesions, accompanied by elevated leukocytes, eosinophils, and C-reactive protein. Diagnostic efforts included a positive LTT to the suspected product, which contrasted with negative skin patch tests. However, further investigation revealed that this LTT positivity was a constitutive false positive, stemming from non-specific lymphoproliferative activity induced by natural ingredients like Euglena, Angelica keiskei, Barley grass, and Chlorella, even in healthy controls.

## 3. Allergic Contact Dermatitis

Dietary supplements and topical formulations are an underrecognized source of allergic contact dermatitis (ACD) because of inconsistent regulation, poor ingredient transparency, and the mistaken belief that "natural" products are inherently safe. A recent systematic review identified emerging sensitizers—including vitamin derivatives (tocopherol, phytonadione, ascorbic acid), herbal extracts (Ginkgo biloba, turmeric, St. John's Wort), and antioxidants (alpha-lipoic acid, resveratrol)—that can cause reactions ranging from localized dermatitis to systemic responses.[77-79] Patch testing often confirms sensitization but can miss allergens that are contaminants, unlisted ingredients, or transformation products formed by oxidation; cross-reactivity is also common. To reduce risk and improve diagnosis, regulatory measures are needed, including clearer ingredient labeling, mandatory adverse-event reporting, premarket allergenicity assessment, and standardized labeling of known sensitizers and botanical components.[77-79]

## 4. Occupational allergy

Occupational allergy is an immune-mediated hypersensitivity caused by workplace exposure to sensitizing agents. It most commonly presents with respiratory symptoms—rhinitis (nasal congestion, sneezing, itching) and asthma (wheezing, shortness of breath, cough)—and may also cause conjunctivitis or skin manifestations such as contact dermatitis or urticaria. Sensitization occurs via inhalation of airborne particles or direct skin contact with substances including cereal flours (wheat, rye), enzymes, animal dander, latex, or chemicals.[80-81] In occupations such as baking, exposure to flours, enzymes, and additives (e.g., psyllium in gluten-free products)[82] can produce "baker's rhinitis" or "baker's asthma," with symptoms that typically worsen at work and improve away from the workplace. Early recognition and avoidance of the offending allergen are essential to prevent progression to more severe or chronic disease.

Stöcker et al.[83] reported occupational sensitization to Aspergillus oryzae–derived lactase in a lactase tablet manufacturing plant: 9 of 13 employees were sensitized by SPT and/or BAT, and lactase-specific IgE (≥ 0.35 kU/L) was found in the sera of the most strongly sensitized workers. Affected employees reported work-related rhinitis, conjunctivitis, cough, dyspnea, and pruritus, primarily during production periods. Immunoblotting identified major lactase protein bands (~65 and 90 kDa), and inhibition assays confirmed specific IgE binding. Correlation among SPT, BAT, and serum IgE supported the diagnosis. Prevention strategies include exposure minimization, engineering and personal protective measures, and regulatory classification to reduce occupational allergy risk—especially in atopic individuals.

## Discussion

This review demonstrates that nutraceuticals and dietary supplements can cause a broad spectrum of HSRs—IHRs, NIHRs, ACD, and occupational allergy—with clinical severity ranging from mild cutaneous eruptions to life-threatening anaphylaxis and SCARs. IHRs were reported most often with injectable or high-exposure formulations (notably parenteral vitamin B1 and vitamin B12), vitamin B complexes, certain prebiotics (short-chain GOS)/probiotics, and plants/animal products (spirulina, natto, royal jelly). Botanicals and Plant-derived products (chamomile, echinacea, flaxseed), were frequently implicated, often via cross-reactivity within botanical families (e.g., Asteraceae, or seed storage proteins). NIHRs and organ-involving syndromes have been linked to agents such as vitamin B12, chromium picolinate, alpha-lipoic acid, DIM, glucosamine/chondroitin, and Euglena-containing products. ACD cases implicate vitamin derivatives, antioxidants, and botanical extracts. Occupational sensitization has been described for bulk materials like psyllium, Aspergillus-derived lactase.

**Figure 1** illustrates the proposed phenotype-driven diagnostic algorithm for suspected HSRs to nutraceuticals and dietary supplements. Diagnostic evaluation requires a multimodal, phenotype-driven approach, but current tools have important limitations. For IHRs, SPT/IDT, BAT, and specific-IgE assays can provide useful supportive evidence: BAT showed high sensitivity/specificity in select studies (e.g., GOS), and positive SPT/IDT have confirmed IgE-mediated allergy in several vitamin and botanical reports (**Table 1**). For NIHRs, patch testing and LTT are commonly used, but LTT may yield false-positives with complex natural extracts (e.g., Euglena) (**Table 2**). Across modalities, diagnostic performance is limited by non-standardized reagents, heterogeneous test concentrations, proprietary or multi-ingredient formulations, and frequent excipient/contaminant involvement (e.g., PEG in cobalamin). These factors reduce reproducibility and complicate interpretation. DPT remains the diagnostic gold standard when safe and feasible, but it carries risk—especially with parenteral exposures or SCAR histories—and must be performed in specialist settings with resuscitation capacity.

Practically, clinicians should (1) prioritize careful product-level assessment (ingredient list, excipients, route, dose, and timing); (2) use SPT/IDT, BAT, patch, or LTT selectively when validated reagents or reliable in-house controls exist; (3) reserve DPT for definitive diagnosis only after risk stratification; and (4) document and report standardized details (formulation, manufacturer, dose, route, test concentrations, and controls) to improve future test validation and epidemiologic understanding.

**Figure 3** summarizes identified risk modifiers, which can be grouped into three main categories: host factors, exposure factors (environmental/occupational factors), and product factors. Key modifiers include atopy; prior environmental or dermal sensitization (e.g., PGA exposure linked to natto allergy); occupational inhalational exposure; route of administration (parenteral forms increase immediate-reaction risk); and excipients or contaminants (e.g., PEG). Cross-reactivity between botanicals and pollens or among plant proteins/legumes further complicates risk assessment.

Regulatory heterogeneity across jurisdictions directly affects safety and clinical care. Many regions regulate supplements as foods rather than pharmaceuticals, permitting market entry without premarket safety or allergenicity testing. This produces variable ingredient transparency, undeclared excipients or contaminants, batch-to-batch variability, and inconsistent quality control—factors that hinder causality assessment and reproducible diagnostic testing and increase patient risk (notably for parenteral or high-concentration products). To mitigate these risks we recommend: mandatory, harmonized adverse-event reporting; clearer standardized ingredient labeling (including excipients and botanical species/chemotypes); premarket allergenicity and contaminant screening for high-risk ingredients or parenteral formulations; and international guidance on validated test reagents and standardized reporting to improve surveillance and reproducibility. **Figure 4** summarizes remaining gaps in diagnosis, which stem not only from regulatory shortcomings but also from consumer and clinician factors.

Limitations of the evidence base must be acknowledged: it is dominated by case reports, small series, and passive pharmacovigilance, with few prospective or large-scale studies. Such sources are prone to publication bias, selective reporting, and absence of denominator data, limiting incidence estimates and causal inference.

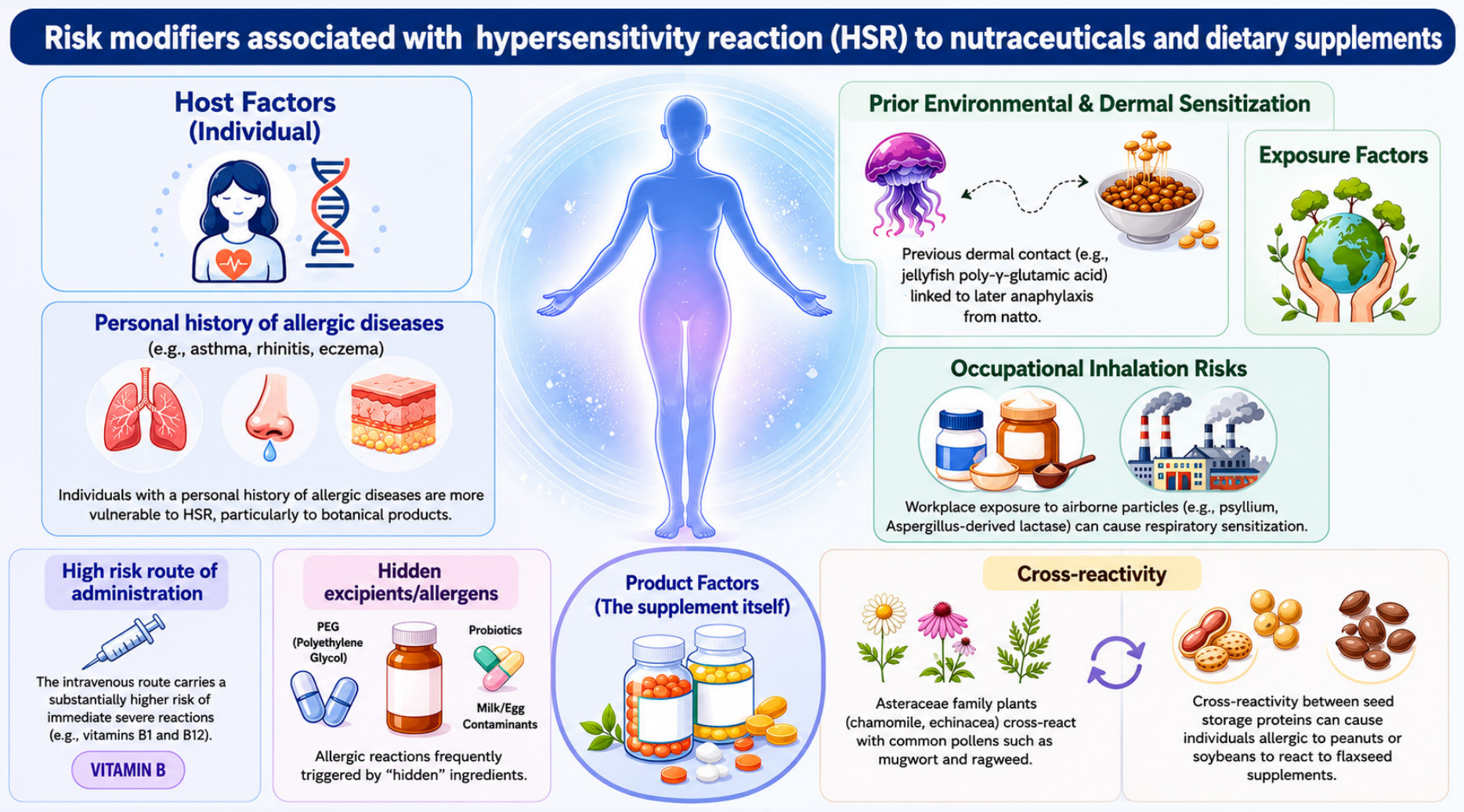


**Figure 3. Risk modifiers associated with hypersensitivity reactions (HSRs) to nutraceuticals and dietary supplements.**

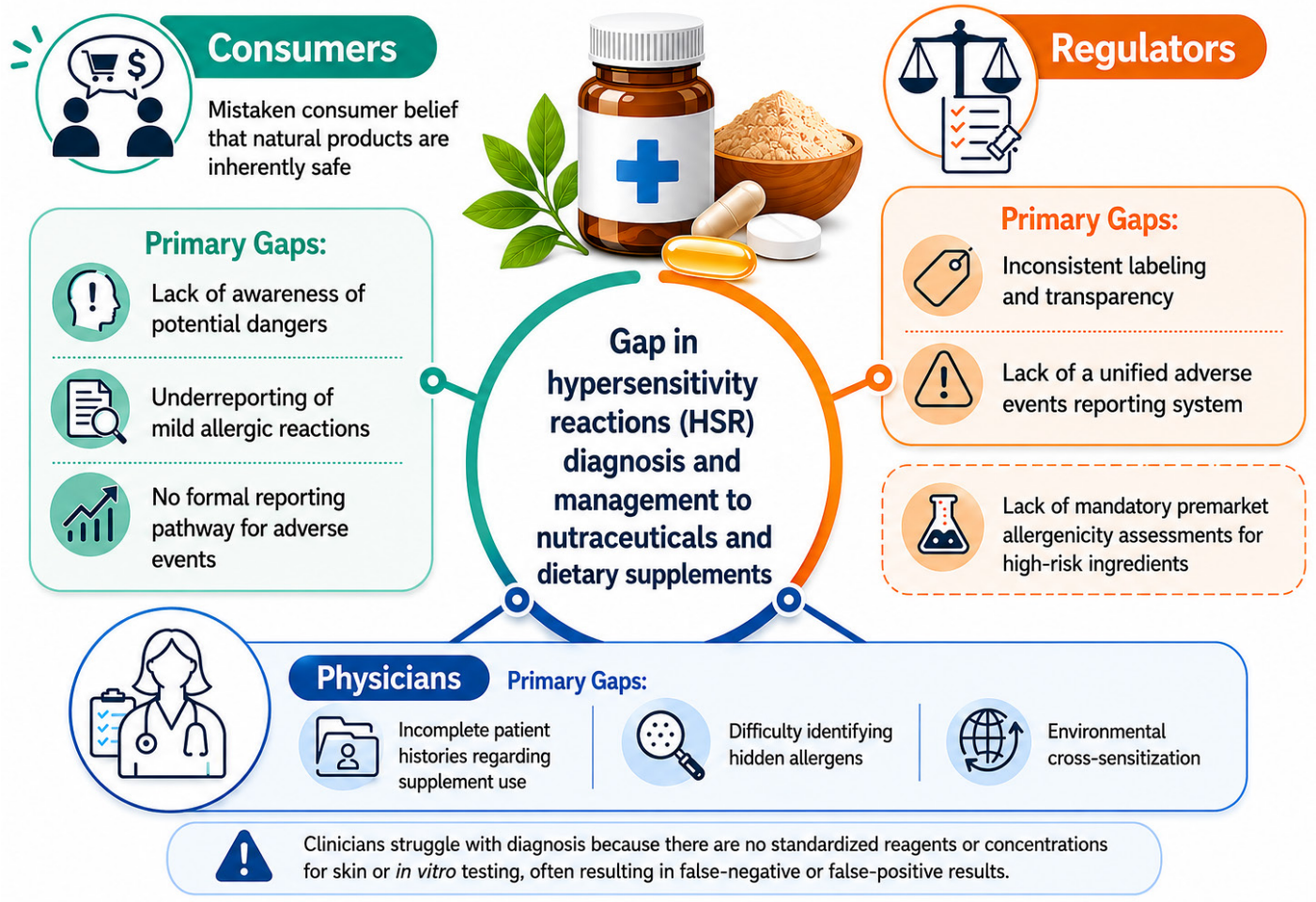


**Figure 4. Gap in diagnosis/management of hypersensitivity reactions (HSRs) to nutraceutical and dietary supplements.**

## Clinical application

HSRs to nutraceuticals and dietary supplements appear uncommon but can be severe. Consumers should be aware of this risk, and clinicians should obtain detailed history of all product use and apply time-appropriate diagnostic algorithms. There is an urgent need for validated, standardized reagents and testing protocols to replace an in-house preparations, and for regulatory measures to improve ingredient transparency and adverse-event surveillance to enhance patient safety.

## Key clinical messages

- Clinicians should always ask about all supplements (brand, formulation, dose, route, timing).
- Distinguish IHR vs NIHR, and mild vs severe HSR, using timing and clinical features to guide testing and management.
- Test selection (phenotype-driven): IHR — SPT/IDT, specific IgE, BAT; NIHR — patch test, LTT.
- Reserve DPT as gold standard only after risk stratification and in specialist settings.
- Consider excipients/contaminants (e.g., PEG) and recognize that parenteral routes carry higher risk.
- Be alert to botanical/seed cross-reactivity and to occupational/environmental sensitization.
- Discontinue the suspected agent immediately for acute or severe delayed reactions; manage per standard protocols.
- Report cases with product/manufacturer/batch, route, dose, and test details to improve surveillance.

## Conclusion

Nutraceuticals and dietary supplements can cause clinically meaningful HSRs across the immediate-to-delayed spectrum. With rising use and the complex composition of many products, stakeholders should strengthen clinical recognition, standardize diagnostic methods, enhance surveillance, and improve regulatory transparency. Future research should prioritize systematic monitoring, validation of diagnostic reagents and protocols, and mechanistic studies to better quantify risk and guide safe use.

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