



Anaphylaxis and alternative medicine: an unexpected association

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Purpose of review

The present review aims to evaluate the use of complementary medicine among patients with allergic disorders, highlighting the risk of adverse reactions, which are often not considered and referred by patients to specialists.

Recent findings

Complementary medicine is often used in clinical practice and preferred by patients as it is considered a natural therapy compared to traditional medicine. This choice is because of various cultural and socioeconomics aspects.

Summary

The use of complementary medicine and its adverse reactions, often as severe as anaphylaxis, is frequently reported in atopic patients, in which a cross reactivity between the natural herbs used and the pollen to which they are sensitized is possible.

Therefore, a personalized approach in atopic patients before the use of natural products is crucial to prevent any adverse reactions.

Keywords

adverse reactions, alternative medicine, anaphylaxis, complementary medicine

INTRODUCTION

Traditional medicine has been used in different cultures around the world for centuries, from the herbs used to treat asthma symptoms by the Aztecs, or inhaled ephedrine used by the Chinese to treat fever and nasal respiratory symptoms. These types of treatments continue to be used by numerous patients. Complementary and alternative medicine (CAM) refers to a wide range of remedies in healthcare practices that are not part of a country's traditional or conventional medicine range and are not fully integrated into the prevalent healthcare system. In some countries, they are used instead of traditional medicine [1]. The number of CAM treatments differs by country, culture, history, and race, and the prevalence of various diseases. An extended list of CAM is described in Table 1 [1]. Many cultures consider CAM a valuable component in their health and wellness store because of a belief that CAM has greater clinical benefits and causes less harm [2]. The World Health Organization (WHO) reported that 80% of the population across all WHO regions use CAM, primarily resorting to herbal remedies. Patients from developing countries more commonly use CAM as their primary treatment whereas patients living in

developed regions use it as a complement to their standard, conventional treatment [3]. The scope of this work review is to analyze the use of CAM and some consequent adverse reactions to lead to greater acknowledgment of recognition, prevention, and management of adverse events.

Patients with chronic or incurable medical conditions such as chronic back pain, chronic renal failure, asthma, and allergies and cancer or arthritis, frequently use CAM [4].

A recent survey carried out with physicians by Land and Wang reported that 81% of respondents

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KEY POINTS

- Adverse reactions to CAM are reported in 60% of patients as primary therapy or parallel treatment for chronic illnesses.
- The risk of anaphylaxis with CAM depends on the intrinsic allergenicity of the substances used, prevalence of use, cross reactions with known allergens, method of administration, and possible contamination.
- There is a need for improvement in the CAM regulations and processing with wider acknowledgment of the treatments contained in CAM, to lay down adequate prevention measures and management of reactions.

had patients who are using CAM therapies over conventional treatments. Patients with asthma and other allergic diseases frequently use vitamin D and C supplementation, fish oils, omega 3, and caffeine and capsaicin with certain degrees of efficacy [5^{***}]. Traditional Chinese medicine formulas such as Pentaherbs have been used for allergic rhinitis and atopic dermatitis to inhibit inflammatory mediator release from mast cells. Other herbs like cinnamon bark are used to inhibit production of prostaglandin D2 resulting in reduced nasal and ocular symptoms [6].

Other commonly used CAM and dietary supplements include chondroitin, coenzyme Q-10, Echinacea species, ginkgo, ginseng, and glucosamine [7]. Well being methods also commonly used are acupuncture, yoga, prayer, meditation, relaxation, and deep breathing [5^{***}]. Homeopathy, home remedies, Ayurveda, and energy are the least commonly used among patients [5^{***}].

In oncology patients, food supplements, vitamins/minerals, and massage therapy are used to reduce side effects and stress to obtain a positive effect in cancer therapy and on the immune system [8].

Table 1. Common CAM used as treatment

Acupressure	Bee products	Light therapy
Acupuncture	Chinese traditional medicine	Ozone therapy
Aromatherapy	Dietary supplements	Reflexology
Ayurveda	Homeopathy	Reiki
Art Therapy	Hypnosis	Yoga

Information based on reference [1].

Abbreviation: CAM, complementary and alternative medicine.

Adverse reactions to CAM have been reported in 60% of patients. These reactions include anaphylaxis because of honey (Table 2), echinacea, and severe dermatitis flares caused by balsam of Peru. Guo *et al.* [9] reported 350 episodes of anaphylactic shock and 10 deaths in patients treated with 17 different types of herbal injections used for cerebrovascular and cardiovascular diseases including *Shen-mai* injection, a traditional Chinese medication that contains mainly ginseng (*Ophiopogon japonicus*) used for coronary heart disease, viral myocarditis and chronic cor pulmonale. The risk of anaphylaxis with CAM depends on the intrinsic allergenicity of the substances used, prevalence of use, cross reactions with known allergens, method of administration and contamination with products that could cause allergic reactions. Many people may also experience side-effects or toxicity reactions either because of the therapy alone or caused by interactions when CAM is used with other medications [4].

Anaphylaxis is a severe systemic hypersensitivity reaction of sudden onset, which may endanger life. It is the most feared allergic reaction and demands rapid recognition and immediate management by healthcare providers [1]. Anaphylaxis symptoms are still poorly recognized in all age groups, sex, and race. Diagnosis is often not made, therefore treatment is delayed [10–12].

Table 2. Reactions reported to frequent CAM

Type of CAM	Reason for treatment	Reactions reported
<i>Andrographis paniculata</i>	Fever and respiratory infections Immunomodulatory roles	Anaphylaxis Angioedema
Echinacea and Asteraceae (Dandelion, ragweed, sunflower)	Prevention and treatment of upper respiratory tract infections	Anaphylaxis
Bee Products (Propolis, honey, bee pollen)	Antibacterial properties, dressings for wounds	Anaphylaxis
Ginkgo Biloba	Improve memory and cognitive function, dementia	Anaphylaxis Allergic rhinitis
Ginseng	Anti-inflammatory properties, used in cancer, asthma, and allergic rhinitis	Occupational asthma Anaphylaxis

Information based on reference [4].

Abbreviation: CAM, complementary and alternative medicine.

Other common reactions that have been described include premature death from cancer in patients who chose CAM and avoid chemotherapy, liver failure caused by dietary supplements and systemic drug reactions with eosinophilia after ingestion of medications supposedly for Lyme disease.

In countries such as Pakistan, Morocco, and Iran, reactions to CAM are reported regularly because these types of treatments are subjected to pharmacovigilance, regulation, and licensing, in the same way as conventional medications [3].

The key to diagnosing anaphylaxis includes recognition of patterns with a sudden onset of symptoms and characteristic signs, minutes to hours after exposure to a potential or known trigger, followed by progression of the clinical condition in the following hours. In patients being treated with CAM, the cause may not be accurately identified, therefore anaphylaxis is under-reported. However, it is important to consider different scenarios for the identification of anaphylaxis, following the amended criteria for the diagnosis of anaphylaxis, proposed by the World Allergy Organization (WAO) Anaphylaxis Committee in 2019 [13,17].

The first scenario: Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:

- (1) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- (2) Reduced BP or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence]
- (3) Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to nonfood allergens

The second scenario: Acute onset of hypotension or bronchospasm or laryngeal involvement (stridor, vocal changes, odynophagia) after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.

Hypotension is defined either as:

- (1) A decrease in systolic BP greater than 30% from that person's baseline
- (2) Systolic BP less than $[70 \text{ mmHg} + (2 \times \text{age in years})]$ in infants and children under 10 years.
- (3) Systolic BP less than $<90 \text{ mmHg}$ in adults.

The patient's medical history is essential for the diagnosis. In addition to the clinical manifestations referred by the patient and a physical examination,

it is important to obtain information on the onset of the reaction, possible triggers, and medications used for the treatment, and the duration and recurrence of the episodes.

The involvement of target organs may vary:

- (1) Skin and mucous membranes (80–90%)
- (2) Respiratory (70%)
- (3) Gastrointestinal (45%)
- (4) Cardiovascular (45%)
- (5) Central nervous system (15%) [13].

Recently recognized symptoms such as chills and fever, which are caused by the release of cytokines from T cells, macrophages, and monocytes, occur most frequently during the administration of chemotherapy and monoclonal antibodies [14].

It has been found that antibiotics such as quinolones and general anesthetics and icatibant activate the new G protein-coupled MRGPRX2 receptor, expressed in mast cells and other cells. [13–14]

Sometimes anaphylaxis can be difficult to diagnose in:

- (1) Patients with vision or hearing limitations.
- (2) Neurological or psychiatric diseases
- (3) Substance abuse
- (4) Autism spectrum disorders
- (5) Attention deficit hyperactivity disorder
- (6) Cognitive disorders [15].

These patients may be less aware of symptoms and anaphylaxis triggers.

Anaphylaxis during pregnancy carries a high risk of ischemia, hypoxia and encephalopathy for mother/child.

It is important to have an action plan for the recognition and treatment of anaphylaxis. If possible, exposure to the triggering agent causing the reaction should be ceased and a circulatory, respiratory, mental, cutaneous and body weight assessment should be performed. Help should be requested from the emergency department or resuscitation team and, subsequently, adrenaline applied in the mid anterolateral section of the thigh at a dose of 0.01 mg/kg at a dilution of 1 : 1000, maximum 0.5 mg in adults and 0.3 mg in children [16]. The dose can be reassessed and repeated 5–15 min later if necessary. The patient should be prevented from standing or sitting and placed in a supine position with elevated limbs or in a comfortable position in case of vomiting or respiratory distress. This is in order to:

- (1) conserve fluids in the intravascular space to avoid distributive shock

- (2) prevent empty vena cava/ventricle syndrome that occurs when a patient is placed in a standing position [16].

When indicated, oxygen with a mask should be provided at 6–8 l/min. The administration of isotonic saline solution at 5–10 ml/kg in adults and 10 ml/kg in children should be performed as required. Table 2 describes the second-line medications used in anaphylaxis, with corticosteroids being effective to avoid biphasic reactions that may occur 8–10 h after the onset of previously resolved symptoms [16]. Other medications used are antihistamines H1 and B2 adrenergic. It is important to emphasize that corticosteroids and antihistamines are NOT the first-line treatment of anaphylaxis and should not be considered as such. Glucagon (at an initial dose of 1–5 mg and 5–15 mcg/min maintenance dose, children maximum 1 mg) may be used in patients with anaphylaxis that do not respond to adrenaline [13,17].

Since 2018, 64% of WAO member states have laws or regulations regarding CAM, specifically herbal medicines. In countries without CAM regulations, New Zealand for example, ‘natural health products’ in oral dose forms are regulated as dietary supplements under the Dietary Supplements Regulations 1985 (under the Food Act 1981). Although these products have other regulations there is no separate category of ‘herbal medicines’ as such. Other countries such as South Africa, share CAM regulations with conventional treatments [3].

In 2005, the document *Toward a pharmaceutical policy* was officially published in Mexico. Conventional pharmaceuticals and herbal medicines are both partly regulated and detailed in the regulation of health commodities, along with allopathic and homeopathic medicines. The WHO European Region has the highest number of countries with a national regulation for CAM, particularly, herbal medicines [3].

CONCLUSION

CAM is used by many patients around the world, either as primary therapy or parallel treatment for chronic illnesses. Numerous allergic reactions including anaphylaxis from CAM have been reported; however, there is still a gap in notifications because of a lack of proper causal agent identification. An improvement in the regulations and processing could lead to greater acknowledgment of the treatments contained in CAM, resulting in adequate prevention measures and management of reactions.

In the light of these results, and of the frequent use of CAM, the allergy and immunology community have a role to play in analyzing each single case of drug anaphylaxis in detail, evaluating also each

single ingredient, spreading the message that the risk of developing an adverse reaction to any ‘classic’ or ‘herbal’ medicine is greater in atopic and asthmatic patients. Therefore, also in the prescription and use of a medicine, a personalized medicine approach should be adopted.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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