

Review article

Review on buckwheat allergy

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Airway exposure to organic dust from cereals may result in both allergic and nonallergic airway diseases. In addition, food allergy to compounds in cereals, e.g., gluten, may occur. Grain-dust lung is one of the oldest occupational diseases to be described in Sweden. In 1555, the last Roman Catholic archbishop of Sweden published the first map of Sweden and wrote a history of the Scandinavian peoples in Europe (1). In it, he noted the risk of throat and airway illness for those employed in threshing and the risk of damage to the throat and other respiratory organs. Buckwheat was then a common crop in Scandinavia. Although occupational health problems arising from exposure to grain dust are well known, the specific health hazards related to handling, processing, and consumption of buckwheat have not been well studied until this century. Another problem is fagopyrism, a toxic photosensitization in animals such as sheep and cattle fed on buckwheat and exposed to sunlight. Its clinical symptoms of itching erythema, constipation, and digestive disturbances of mild to serious degree have long been described in the literature. This is a toxic reaction from fagopyrin, a polyaromatic derivative of naphthodianthrone, and is not related to buckwheat allergy (2).

Buckwheat (*Fagopyrum esculentum*) is not taxonomically related to wheat, but is sometimes used as a substitute for it. Buckwheat can be cultivated under poorer conditions than rice, at high altitudes, and both grain and leaves can be used as food (3). It is grown in both the East and the West, in Asian countries such as China, Korea, Tibet, Nepal, and Bhutan as well as in Russia, Slovenia, Italy, Canada,

and the USA. The advantages of buckwheat may make it a crop of greater importance in the future. There is also a growing interest in buckwheat products as health food and as a substitute for wheat flour in gluten-allergic persons. In Japan, it is already commonly used in dishes such as noodles, dumpling, and bun, but it is also used as pillow stuffing. In other countries, it is often used in batter for cakes or pancakes.

Allergy to buckwheat was first reported in the scientific literature in 1909 (2). The pathomechanism of this allergy is type I; therefore, it is an IgE-mediated, immediate-type reaction. Because of its potentially allergic properties, exposure conditions during postharvest treatment, storage, and refining and cooking of buckwheat should be controlled to minimize airborne exposure. Small amounts can provoke serious symptoms in all types of exposure, including oral, in a sensitized subject, and avoidance is the only sure prevention (4).

Most of the literature on this topic consists of case studies, mainly on buckwheat food allergy among children. There are also some epidemiologic studies on occupational buckwheat allergy. In addition, there has lately been research on buckwheat immunology, identification of allergens, IgE-binding epitopes, and the mechanisms of antigenic cross-reactivity.

Case studies on buckwheat allergy

In 1909, Smith described a buckwheat-allergic adult patient who suffered from symptoms of asthma, allergic rhinitis, urticaria, and angioedema (2). The allergic reactions were provoked by

ingestion of small amounts of buckwheat flour. In 1913, Peshkin demonstrated a positive skin prick test to an extract from buckwheat in an allergic child (5). In 1931, Rowe demonstrated 27 positive skin prick reactions among 500 consecutive cases in the USA (5.4% positive) among patients referred to his clinic (6). Thirty years later, Horesh published another study on buckwheat allergy in US children (7). He identified 36 cases of buckwheat allergy at his clinic in Cleveland, OH, USA, out of a total of 514 patients. He found the percentage of buckwheat-sensitive children to be 1% in his patient material. He also stated that the exposure to buckwheat allergens might increase in the USA as buckwheat came to be more commonly used.

Since the 1960s, a series of Japanese studies on buckwheat allergy has been published. In one early study, cases of buckwheat allergy were described by Nakamura et al. (8). An important Japanese paper on buckwheat allergy was published by Nakamura & Yamaguchi in 1974/1975 (9). Cases of buckwheat allergy were thoroughly studied. Hypersensitive symptoms included asthmatic attacks, urticaria eruption, gastrointestinal disorders, nasal symptoms, and conjunctival congestion. Routes of exposure included both mouth and airway. The pathomechanism was type I; therefore, it was an IgE-mediated, immediate-type reaction. The author also concluded that the antigenicity of buckwheat is extremely strong, and that hyposensitivity treatment with buckwheat extracts should not be given because of the risk of severe and dangerous reactions.

In addition, Nakamura & Yamaguchi administered a nationwide questionnaire screening on buckwheat allergy in Japan (9). They mailed questionnaires to every department of internal medicine, pediatrics, otorhinopharyngology, and dermatology at university hospitals in the country. This survey yielded 169 identified cases of buckwheat allergy. The patients were thoroughly examined with skin test, scratch test, nasal test, skin prick test, inhalation provocation test, dietary test, and measurement of eosinophils in peripheral blood.

Most patients (75%) had a raised level of blood eosinophils. Most of them were young children; 14% were adults aged 20 years or more. It was also noted that most were male; there was a male : female ratio of 1.64. Food allergy to buckwheat was the most common type of allergy, but as many as 60% also reported symptoms at exposure through the airways. The most common symptom was asthmatic attack in relation to buckwheat exposure; 139 patients (82%) suffered from buckwheat asthma. Less common were nasal symptoms

(23%), eye symptoms (13%), urticaria (45%), and gastrointestinal symptoms (33%). In 18 of the patients, anaphylactic shock at exposure to the buckwheat allergen occurred.

Occupational buckwheat allergy

Allergy to buckwheat has been reported as one cause of occupational asthma among workers in noodle shops in Japan (10). Another Spanish report examined and documented a case of occupational buckwheat allergy (11). A 29-year-old woman developed sneezing, rhinorrhea, and nasal itching shortly after she began her work of making buckwheat crepes. Four years later, she had dyspnea, wheezing, and contact urticaria. In the next stage, she suffered nausea, vomiting, gastric pain, and urticaria a few minutes after she ate buckwheat crepes. At provocation, buckwheat flour produced an allergic reaction if in contact with the digestive and cutaneous systems. The authors demonstrated IgE against buckwheat flour in the patient's serum by means of specific tests; e.g., the histamine release test. The authors remarked that although buckwheat flour is used in the baking industry in most Western countries, few reports of allergy exist.

Schumacher et al. described six cases of buckwheat allergy among adults in Switzerland (12). Two of the cases were occupational asthma due to buckwheat exposure in a health-food shop, and a bakery, respectively. Sensitization was proven by positive skin prick tests and specific IgE (RAST). In another case report from the USA, buckwheat-induced anaphylaxis after ingestion of buckwheat crepes was demonstrated in a woman who had undergone occupational exposure 4 years earlier (13). She had manufactured cushions and pillows with filling of buckwheat husk and kapok fibers.

There is little information in the literature from epidemiologic studies on manifestations of buckwheat allergy. In 1983, we published a study on 28 persons in a Swedish company importing, preparing, and distributing plant products used in spices and in health-food products (14). The imported raw material arrived in sacks, and was repacked in separate package rooms into smaller packets weighing 0.25–1 kg. Buckwheat, which caused the most adverse reactions, was delivered in 25-kg sacks and was repacked, but not ground. All 14 men and 14 women, aged 17–65 years, participated in the study. The employment period ranged from 2 months to 20 years, and eight subjects had worked less than 1 year. Twenty-five of the subjects (89%) were smokers. Thirteen subjects experienced rhinitis, asthma, skin itching, and conjunctivitis related to buckwheat exposure. The reactions usually appeared within 1 h after exposure. Allergy tests

such as Phadebas RAST (15) were performed on 25 subjects against antigens from buckwheat and on 15 subjects against antigens from soybean flour. Prick tests and patch tests against buckwheat were also performed. Positive allergy tests were seen in seven (28%) of the 25 tested subjects. Atopic heredity (eczema, hay fever, asthma) was found in only six subjects (21%).

In the Swedish study, airborne dust levels were measured by personal sampling in the breathing zone of the workers at different types of operations (14). The highest dust levels were measured at grinding of chickpeas and coriander (3.6 and 6.4 mg/m³, respectively). Lower dust-exposure levels were measured at packing of buckwheat and rice (1.7 and 0.9 mg/m³, respectively). The dust exposure while packaging buckwheat was not high, as compared to existing permissible exposure limit values (PEL) for organic dust in Sweden (5 mg/m³) (16).

Allergenic properties and other features and problems in buckwheat food hypersensitivity and allergic asthma

The immunologic properties of buckwheat have been identified by new techniques using the immunoblotting method, radioallergosorbent test (RAST), and RAST-inhibition assay (17, 18). A 24-kDa buckwheat protein (BW24KD) was the most frequently recognized allergenic component, binding to IgE antibodies from 100% of the patients' sera. Of subjects ($n=41$) with positive IgE RAST to buckwheat antigens, 85.4% were positive to BW24KD. All patients with positive prick tests for buckwheat antigens were positive for BW24KD. The RAST-inhibition assay using patients' sera showed positive IgE antibodies to both whole-buckwheat extract and BW24KD. There was effective inhibition in a dose-dependent manner between BW24KD and buckwheat extract. These findings indicate that the major allergenic properties in buckwheat were to be found in the BW24KD protein.

Buckwheat is used instead of gliadin-containing cereals such as wheat by gluten-allergic patients (celiac disease) (19). The enzyme-linked immunosorbent assay (ELISA) for quantification of cereal proteins toxic in celiac disease is of value to plan an elimination diet. An inhibition ELISA has been developed, with a purified, polyclonal prolamin antibody reacting with gliadin-like polypeptides in the food. The buckwheat flour was thus analyzed for antigen content. An amount of 39.5 µg gliadin-like polypeptides per gram flour was measured, corresponding to 0.06% of the gliadin content in wheat flour. The antibody did not react with maize, millet, rice, or soybean prolamines. The detection

limit of the assay was 1 ng antigen, ensuring a high degree of sensitivity.

Recently, it has been found that cross-allergenicity between rice and buckwheat occurs especially (20). This resulted in an inhibited immediate hypersensitivity reaction (IHR) in 28 out of 48 subjects with positive RAST values for both buckwheat and rice. RAST values for buckwheat and rice were significantly correlated with each other in the IHR-negative group, but not in the IHR-positive group. An effective dose-dependent inhibition was obtained in a RAST-inhibition assay between homologous combinations of inhibitor and disk antigens such as rice and rice or buckwheat and buckwheat. The IHR-positive group showed no significant RAST inhibition between heterogeneous combinations of rice and buckwheat antigens, whereas the IHR-negative group showed a significant decrease in IgE binding even in the RAST inhibition between heterogeneous combinations of rice and buckwheat antigens. The conclusion was that IgE antibodies from IHR-negative subjects might recognize the epitopes on buckwheat antigens which cross-react with rice antigens. In 1991, a similar study concluded that subjects without IHR to buckwheat showed higher IgE RAST values for rice than those with IHR, whereas there were no differences in IgE-RAST for *Dermaphagoides pteronyssinus*, egg white, and cow's milk between groups with and without IHR (21).

The difficulties in identifying food hypersensitivity with IgE antibodies that cross-react with diverse products such as vegetable foods, pollen, and Hymenoptera venom have been shown by Aalberse et al. (22). IgE identified in some human sera reacted with an antigen in various unrelated foods such as potato, spinach, wheat, buckwheat, peanut, and honey. The antigen could also be found in pollen, and *in vitro* it reacted also with bee and vespid venom and was sometimes induced by Hymenoptera stings.

Problems with accurate and safe diagnosis of food hypersensitivity including buckwheat allergy were demonstrated by Matsumoto & Murakami in 1991 (23). In 41 children with suspected IgE-mediated food allergy, oral exposure to hen's egg, cow's milk, chicken, buckwheat, red bean, salmon, and common dolphin was effectuated. Seven showed an anaphylactic skin reaction (systemic urticaria and/or angioedema) to the foods. The authors recommend diagnosis with the oral Prausnitz-Küstner (P-K) test in combination with RAST instead. The sera that had RAST scores of 3 or greater were negative in the oral P-K reaction in 26 out of 36 tests, and the sera that showed positive oral P-K reaction to buckwheat or chicken were zero in the RAST scores. It was suggested

that a soluble, e.g., histamine-releasing, factor in addition to the IgE antibody might be involved in the oral P-K reaction, and that the RAST technique does not always recognize the food antigens digested during the absorption process *in vivo*.

Allergic asthma to buckwheat in children is a serious problem in some Asian countries such as Japan. A study on total serum IgE and specific IgE antibodies in children with asthma found that in a total of 342 asthmatic children, the median and range of serum IgE were 1.050 IU/ml and 20–10 000 IU/ml, respectively (24). Positive rates were highest for mites and house dust (87–91%) and lowest for milk, dog, buckwheat, and egg (2–8%). In general, patients with higher RAST scores had higher serum IgE levels (18).

Treatment with ketotifen has been tried experimentally but is not generally accepted. In 64 patients with bronchial asthma, it was shown effective in 50% and very effective in 6% (25). In allergy to house dust and buckwheat, it seemed effective in 5/6 patients and in all three with buckwheat allergy, respectively. Ketotifen was considered to inhibit type I allergic reactions caused by specific allergens and clearly IgE-mediated reactions.

Conclusions

The lack of epidemiologic studies on buckwheat allergy makes it difficult to estimate the prevalence or incidence of allergic manifestations to buckwheat in the population in different countries. As indicated by available case reports, a large proportion of the patients are allergic children, and food allergy is a common type of allergy. There are also both children and adults with asthmatic reactions at airway exposure to low levels of buckwheat dust. Domestic exposure during preparation of food may be one cause of this allergy, and allergen exposure from buckwheat used in pillows may also be important in some countries.

In conclusion, as indicated by several case reports, buckwheat contains very potent allergens, which may cause various types of allergic reactions, including asthma and anaphylactic shock. The major allergen seems to be a 24-kDa protein (BW24KD), and the pathomechanism is type I, meaning an IgE-mediated, immediate-type reaction.

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