

Review Article

Allergic risks of consuming edible insects: a systematic review

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Abstract

The expected future demand for food and animal-derived protein will require environment-friendly novel food sources with high nutritional value. Insects may be one of such novel food sources.

However, there needs to be an assessment of the risks associated with their consumption, including allergic risks. Therefore, we performed a systematic review aiming to analyse current data available regarding the allergic risks of consuming insects. We reviewed all reported cases of food allergy to insects, and studied the possibility of cross-reactivity and co-sensitisation between edible insects, crustaceans and house dust mites. We analysed a total of 25 articles – eight assessing the cross-reactivity/co-sensitisation between edible insects, crustaceans and house dust mite; three characterizing allergens in edible insects and 14 case reports, describing case series or prevalence

studies of food allergy caused by insects. Cross-reactivity/co-sensitisation between edible insects and crustaceans seems to be clinically relevant, while it is still unknown if co-sensitisation between house dust mites and edible insects can lead to a food allergy. Additionally, more information is also needed about the molecular mechanisms underlying food allergy to insects, although current data suggest that an important role is played by arthropod pan-allergens such as tropomyosin or arginine kinase.

Keywords: Allergenicity; case reports; cross-reactivity; crustacean; entomophagy; house dust mites; tropomyosin

Abbreviations: AK – Arginine Kinase; BAT – Basophil activation test DBPCFC – Double Blind Place Controlled Food Challenge; GADPH – Glyceraldehyde 3-phosphate dehydrogenase HDM – House Dust Mites; HEX1B – Hexamerin 1B precursor; SPT – Skin Prick Tests

1. Introduction

In the next decades, it is expected that meat production and consumption will reach unsustainable levels [1], not only due to the predicted population growth but also because of the spread of Western dietary habits to developing countries [2]. Consequently, this higher livestock use will likely result in increased greenhouse gas emissions [3] and economic costs [1]. This prompts the need for a healthier and more environment-friendly diet [2]. Several approaches have been envisioned in order to respond to the growing demand for food (especially animal-derived protein), one of which concerns the use of novel food protein sources [4]. Insects represent one of such novel food sources, as they have a high content in high quality proteins, polyunsaturated fatty acids, iron, zinc, riboflavin, pantothenic acid, biotin and folic acid [5, 6]. Consuming insects can also have environmental advantages, as there will be reduced pesticide use [7] and smaller land areas will be able to produce the same quantities of

protein [8]. This results in fewer greenhouse gas emissions [8], higher efficiency in feed conversion and the ability to convert organic side stream into high value protein products [9].

Entomophagy (the use of insects as food) dates back to the early development of humans [10]. Currently, it is practiced in 113 countries (mainly in Africa, Asia and Latin America) and over 2,000 species are consumed, with representatives of all groups being eaten [11]. On the other hand, in Western countries, entomophagy has always been marginalized [12]. However, this situation is changing. Recently, the European Union has legally defined insects as novel food sources, identifying several species of insects with potential to be used for human consumption, including the house cricket (*Acheta domesticus*), field cricket (*Gryllus assimilis*), banded cricket (*Gryllodes sigillatus*), migratory locust (*Locusta migratoria*), yellow mealworm (*Tenebrio molitor*), lesser mealworm (*Alphitobius diaperinus*), wax moth (*Galleria mellonella*) and silkworm moth (*Bombyx mori*) [4, 13-15]. Recent studies from Cunha and collaborators [16, 17] have shown that, within Western cultures, consumers may be segmented within four groups going from strong acceptors to strongly disgusted with the concept of insect eating or with the use of insects as feed, presenting relevant perspectives on the future acceptance of insects in the diet of Western consumers.

When dealing with novel food sources, it is imperative to assess possible risks, including their allergenic potential. Most cases of insect allergy are caused by stings from insects belonging to the order *Hymenoptera* (e.g. wasps, bees) [18], although bites by blood-sucking insects, poisonous spines or hairs and defensive secretions can also elicit allergic reactions. Additionally, insects or volatile substances emanating from them can also act as aeroallergens [19-21] - cockroaches are one of the major sources of indoor allergens [22] and there are several reports where occupational handling of insects that are used for food and feed (such as the yellow mealworm [23], crickets [24] or locusts [25]) can lead to species-specific sensitization and to development of inhalant allergies. When studying the allergenic potential of novel protein sources it is important to study its taxonomy

relationship with known allergenic sources in order to identify possible groups at risk [26]. In regard to insects consumption the allergenic risk might principally arise due to a possible cross-reactivity with other arthropods, especially crustaceans (one of the most common triggers of food allergy in the Western world [27]) and HDM (one of the most frequent sources of indoor allergens responsible for the development of allergic respiratory reactions [28]). Edible insects and crustaceans are much closer taxonomically than what was previously thought [29] and cross-reactivity seems to be a real possibility. In fact, cross-reactivity between non-edible insects (e.g. cockroaches) and crustaceans/HDM has already been studied with tropomyosin and AK being identified as arthropod cross-reacting allergens [30-34]. Therefore, particularly in patients with food allergy to crustaceans or with allergy to HDM, the risk of allergic reactions after consuming insects needs to be systematically assessed.

Considering these potential allergic problems associated with entomophagy, the objectives of this review are 1) to evaluate the cross-reactivity and co-sensitization between edible insects, crustaceans and HDM, 2) to assess what allergens are responsible for cross-reactivity or co-sensitization, assessing their clinical significance, and 3) reviewing and analysing all reported cases of food allergy to insects.

2. Methods

We conducted a systematic search on PubMed/Medline, Scopus and Web of Science, on October 2016. We used the query (insect OR mite* OR carmine OR cochineal OR cockroach OR arthropod OR crustacea* OR silkworm OR locust OR grasshopper OR cricket OR mealworm OR moth OR beetle) AND (allerg* OR hypersensitiv* OR anaphyla* OR cross-reactiv*) AND (food OR edible OR consumption OR entomophagy OR ingesti* OR occupati* OR consum* OR eat*). We did not apply any restriction based on the date of publication or the language of the articles.

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Additionally studies already known to the authors were also considered for inclusion based on criteria described below. We also screened the references of included studies and review papers concerning entomophagy in order to identify potentially relevant studies.

Inclusion and exclusion criteria

We included original articles studying cross-reactivity and co-sensitisation between insects, crustaceans and HDM. Articles identifying and characterizing allergens of edible insects were also included. Additionally, we included case reports and case series describing allergic reactions following the intentional ingestion of insects, as well as studies assessing the prevalence of such reactions.

We excluded articles concerning the detection of allergens in insects without potential to be used for human consumption in the EU (e.g. cockroaches). We also excluded articles only assessing inhalant allergies to insects, as well as allergic reactions due to stings, venom or products derived from insects (such as honey, silk or carmine).

Study selection and data collection

Two authors independently screened the search results by title and abstract reading of the retrieved articles. The full texts of the selected articles were further analysed by two authors independently. Among studies selected after full-text reading, data was collected regarding their year of publication, study design, insects, allergens and cross-reactivities studied, and major conclusions. Any disagreement was solved by the consensus.

3. Results

A total of 8186 articles were retrieved from database searching and, after duplicates removal, 4793 articles were targeted for title and abstract reading. After this initial analysis, 233 articles were selected for full text reading, of which a total of 24 original articles were included in this systematic review. One article identified through screening references of review papers concerning entomophagy was also included (fig.1).

Of these 25 articles, 8 studied the cross-reactivity/co-sensitisation between edible insects, crustaceans and HDM [35-42], 3 identified and characterized allergens of edible insects [43-45], 10 were cases reports or case series of food allergy caused by insects (8 case reports [46-53], and 2 case series [54, 55]), 3 assessed the frequency of anaphylaxis caused by entomophagy [56-58] and 1 assessed the prevalence of allergy among insect-eaters [59].

3.1 Cross-reactivity/co-sensitisation and detection of allergens

The results of the experimental studies assessing cross-reactivity/co-sensitisation between allergens in edible insects and those in other arthropods (crustaceans and HDM), or identifying allergens in edible insects are summarized in table 1. We found 8 studies focusing on cross-reactivity/co-sensitization between insects with potential to be used for human consumption in the EU and crustaceans/HDM [35-42]. These studies refer to the yellow mealworm (*Tenebrio molitor*) [35, 36, 41, 42], field cricket (*Gryllus bimaculatus* [38, 40], *Gryllus campestris* [38]), house cricket (*Acheta domesticus*) [38], Bombay locust (*Patanga succinta*) [39], grasshopper (*Mecopoda elongata*) [37], lesser mealworm (*Alphitobius diaperinus*), and super mealworm (*Zophobas atratus*) [41]

The role of tropomyosin as an arthropod cross-reacting allergen was confirmed in one article [37]. In this article, it was found that sera from nine shrimp-sensitive subjects reacted to a 38/40 kDa protein band with extracts from insects (including the grasshopper *Mecopoda elongata*) on immunoblot. Cross-reactivity was further established by performing immunoblot inhibition with recombinant shrimp tropomyosin.

Verhoeckx *et al* [42] demonstrated on immunoblot that sera from a majority (six out of seven) of crustacean/HDM Derp 10 (tropomyosin) allergic patients showed IgE-binding to yellow mealworm extracts. Furthermore all tested patients (n = 5) had a positive indirect BAT in response to yellow mealworm extracts. According to this study, the major cross-reactive yellow mealworm proteins were identified as being AK and tropomyosin although other proteins such as α -tubulin, β -tubulin, actin, fructose-biphosphate aldolase, myosin light chain and Troponin-T were also identified. Additionally, the authors predicted the allergic potential of yellow mealworm proteins using Allermatch – a protein can be considered potentially allergenic when it shows more than 35 % identity with a known allergen within a window of 80 amino acids or more. Proteins identified as potential yellow mealworm allergens were α -amylase, putative trypsin-like proteinase, putative serine proteinase and cockroach allergen-like. Broekman and Verhoeckx *et al* [36] assessed the clinical significance of cross-reactivity between yellow mealworm and shrimp. In this study, 15 patients allergic to shrimp and shrimp/HDM were tested in a DBPCFC trial to assess allergenicity with yellow mealworm - all patients were sensitive to mealworm (positive SPT) and 13 (87%) had a positive DBPCFC with mealworm. The authors also found that for the vast majority (14 out of 15) of patients they recognized either mealworm tropomyosin/AK on immunoblot, and that the threshold for objective symptoms (216 mg) was equal or lower to the amount of mealworm protein contained in currently produced snacks.

The allergenicity of mealworm was further studied by two studies, which confirmed that IgE from patients allergic to HDM or crustaceans is able to bind to proteins from unprocessed extracts of yellow mealworm [35, 41], giant mealworm and lesser mealworm [41]. These two studies also assessed the effects of processing methods [35, 41]. According to Broekman *et al*, heat processing changes the solubility of mealworm allergens like tropomyosin or AK [35]. Although the authors were not able to assess with certainty the effect of thermal processing on IgE-binding capacity of mealworm proteins, this processing method did not change IgE cross-linking functionality, as confirmed by SPT and BAT [35]. Similar results were also found by van Broekhoven *et al* [41], who

identified tropomyosin from yellow mealworm to react with IgE from crustacean allergic patients. Boiling or *in vitro* digestion did not significantly alter tropomyosin IgE-binding capacity, while frying eliminated it. Analysis of identified tropomyosin with Allermatch further confirmed the allergenic potential - 100 % of segments of 80 or more amino acids showed 35% or greater identity to known allergic tropomyosins. Yellow mealworm tropomyosin also had high amino acid sequence identity (60-85%) with known arthropod tropomyosins. The authors also used sera from HDM-allergic patients and the processing methods significantly diminished IgE-binding capacity of identified proteins (predicted long form paramyosin, α -amylase, actin, a predicted larval cuticle protein, hexamerin 1B precursor and heavy chain muscle myosin). Phiriyangkul *et al* [39] also assessed the effect of thermal processing on the allergenicity of an edible insect (Bombay locust) and was performed with pooled sera from 16 prawn-allergic subjects. Like the studies performed with yellow mealworm, thermal processing did not eliminate IgE-binding capacity of allergens identified on the insects extracts, although it altered the intensity and allergens identified. In unprocessed Bombay locust extracts AK, Hexamerin and enolase were identified as IgE-binding proteins. Frying eliminated IgE-binding capacity of AK and decreased IgE-binding capacity in HEX1B and enolase. Furthermore, on frying extracts it was possible to identify two new IgE-binding proteins that did not appear on unprocessed extracts: GADPH and pyruvate kinase.

Srinroch, *et al* [40] performed a study focusing on the allergenicity of the field cricket *Gryllus bimaculatus*. Using pooled sera from 16 prawn-allergic patients the authors identified AK and HEX1B as IgE-binding proteins on *Gryllus bimaculatus* extracts. Analysing band intensity of the IgE-binding proteins AK was identified as the major allergens and HEX1B as a novel minor allergen. However, one other study [38] performed in a patient with inhalant allergy to three species of crickets (*Acheta domesticus*, *Gryllus bimaculatus* and *Gryllus campestris*) found no cross-reactivity with prawn or mite *Dermatophagoides pteronyssinus* through EAST inhibition assays.

Three studies [43-45] have been performed in silkworm-sensitive individuals, and focused on identifying allergens responsible for silkworm allergenicity. Liu *et al* [44] not only identified AK as a major allergen, but also found that this allergen cross-reacted with AK from cockroaches and that it has a high sequence homology with AKs that have been associated with allergenicity like shrimp AK. Zhao *et al* [45] identified chitinase and paramyosin as silkworm pupa's allergens while speculating that these proteins could potentially be cross-reactive due to their high sequence homology with their homologues in HDM. Jeong *et al* [43] focused on heat-stable allergens, identifying a 27-kDa glycoprotein as a heat stable IgE-binding component. However, specific IgE to recombinant 27-kDa glycoprotein was only detected in five of the 15 subjects allergic to silkworm pupa. Additionally, no cross-reactivity was identified since HDM-sensitized patients did not demonstrate IgE reactivity against this protein.

3.2 Case reports, case series and prevalence studies

Regarding articles reporting allergic reactions following intentional consumption of insects, we found three studies that assessed the frequency of anaphylaxis caused by entomophagy [56-58] and one study of prevalence of allergy among insect-eaters [59], eight case reports [46-53], two case series [54, 55] (table 2), The species reported to have caused allergic reactions were locusts, grasshoppers [56-58], silkworm (*Bombyx mori*) pupae [48, 55, 56], vegetable worm (*Cordyceps sinensis*) [54], mopane worms (*Imbrasia belina*) [49-51], yellow mealworm (*Tenebrio molitor*) [46, 47], cicadas [52, 56], bee pupae, bee larvae, moth (*Clanis bilineata*) [56] and sago worms (*Rhynchophorus ferrugineus*) [53].

3.2.1 Prevalence studies

Three articles [56-58] reported the prevalence of anaphylaxis caused by entomophagy. In a review [56] of 358 cases of anaphylactic shock caused by food ingestion published in Chinese literature, 63 (17.3%) were caused by insect consumption; locusts (7%) and grasshoppers (7%) were the species

that caused the most reactions. Another study [58] performed during a two-year period in a tertiary-care hospital in Thailand, found that, of 36 cases of food-induced anaphylaxis, seven (19.4%) were caused by consumption of fried grasshoppers and locusts. Interestingly, one of the patients that had anaphylaxis to consumption of fried insects developed shrimp-induced anaphylaxis a few months later. In a similar study [57] performed in an University Hospital in Thailand, of 24 cases of food-induced anaphylaxis, one (4.2 %) was caused by ingestion of fried insects (species not determined).

Barennes *et al* [59] assessed the prevalence of food allergy to insects amongst insect-eaters. The authors performed a questionnaire addressed, among others, socioeconomic characteristics of the consumers, types of insects consumed, frequency of consumption and reports of side effects. This study was conducted in Laos, and included 1059 subjects that had previously eaten insects, of whom 81 (7.6 %) reported allergic reactions following insects' consumption. Unfortunately, the species of insects that caused the allergic reaction was not specified, although the subjects in this study identified stink bugs and grasshoppers as causative agents of allergic reactions. Additionally, there were no reports of fatalities or even severe anaphylaxis to consumption of insects.

3.2.1 Case reports and case series

Silkworm pupae are widely consumed in China and there are several reported cases of food allergy to their consumption, not only in China [55] but also in the U.S.A [48]. Ji *et al* [55] reported the case of a French man visiting China with a history of allergic rhinitis that went into anaphylactic shock after consuming silkworm for the first time. The same article reviews 13 prior cases of severe anaphylactic reactions occurring in China, and caused by silkworm pupae consumption. In all cases the patients had no previous history of allergic shock and were consuming silkworm pupae for the first time. Gautreau *et al* [48] reports two simultaneous cases of anaphylaxis following ingestion of silkworm pupae on two Nepalese immigrants in the U.S.A. The subjects were father and son and both were consuming silkworm pupae for the first time and neither had antecedents of other allergic diseases.

The vegetable worm uses the silkworm pupa as their host and can also be used as food. There is one article [54] reporting five cases of food allergy following consumption of the vegetable worm, with three patients reporting generalized urticaria. All patients had associated allergic diseases such as respiratory allergy ($n=4$), chronic urticaria ($n=1$), and food allergy to seafood ($n=1$). Interestingly, all subjects were sensitized to silkworm pupa (positive SPT) and, after ingesting silkworm, they developed symptoms similar to those elicited after vegetable worm consumption. Cross-reactivity between these two species was further confirmed with competitive ELISA inhibition tests. Besides these cases, we only found another case [52] where a subject with known food allergy to shellfish developed food allergy following consumption of cicadas.

There are also reports of three cases [49-51] of food allergy following ingestion of mopane worms, all occurring in Botswana. In one of those cases [51], the patient had no history of atopy and had eaten mopane worms all her life without developing symptoms of food allergy. In the other two cases [49, 50] the patients not only had history of allergic diseases (namely rhinitis and conjunctivitis) but were also sensitized to common allergens such as HDM.

There are three described cases [46, 47] of subjects developing food allergy to yellow mealworm, all of them with previous constant exposure to that species. In two of those cases [46] oral challenges to shrimp were performed and the subjects showed no symptoms. In all cases, subjects were sensitized to common allergens and, in two cases (both with symptoms of inhalant allergy to yellow mealworm), the subjects were sensitized to HDM.

Although there were no reports of fatalities following insect consumptions it is noteworthy to mention one peculiar case [53] where a patient developed Takotsubo cardiomyopathy following an anaphylactic reaction resulting from the ingestion of sago worms [53].

4. Discussion

In this systematic review, we observed that all listed studies assessing cross-reactivity/co-sensitisation between crustaceans and edible insects identified either tropomyosin or AK (known arthropod pan-allergens) as cross-reacting allergens. Some case reports and a study performing a DBPCFC provided evidence that supports the hypothesis of cross-reactivity between edible insects and crustaceans has some clinical significance. Nevertheless, there is substantial lack of information regarding the allergenicity of edible insects and the clinical context in which allergic reactions to insects preferentially occur.

As previously mentioned, tropomyosin and AK have been described as arthropod pan-allergens – these molecules are responsible for cross-reactivity between insects and other arthropods [30-34], and both have been described and characterized as insect allergens (e.g. cockroaches) [60-62]. The studies performed with edible insects [35-37, 39-42] further confirmed the role of tropomyosin and AK as cross-reacting allergens with crustaceans, although other known arthropod allergens (GADPH, myosin light chain, fructose-biphosphate aldolase, actin, α -tubulin, β -tubulin) have been identified. Hexamerin was also identified as a cross-reacting allergen with crustaceans in studies performed with the Bombay locust [39] and field cricket *Gryllus bimaculatus* [40]. Although hexamerin is not identified as a crustacean allergen, they belong to the same superfamily [63] as hemocyanin which is a crustacean allergen. In addition, yellow mealworm tropomyosin shares some important characteristics of food protein allergens [64], as it is an abundant protein [65], and appears to maintain its allergenic activity after thermal processing and *in vitro* denaturation [35, 41]. These characteristics are similar to those of the crustaceans' tropomyosins [66, 67]. After analysing yellow mealworm tropomyosins with Allermatch it was possible to confirm its allergenic potential given that 100 % of tropomyosin segments of 80 or more amino acids showed 35% or greater identity to known allergic tropomyosins (including tropomyosins from shrimp) [41]. The tropomyosins identified also had a

high amino acid sequence identity (60 – 85 %) with shrimp tropomyosins [41]. Tropomyosins in mites (78,5%-81,7%), cockroaches (82,4%), midge (chick 10 – 78,5%), parasites (Anisakis-72.9%) and silverfish (Lepidoptera-67.9%) also had similar sequence identity with shrimp tropomyosin Penaeus [68]. Linares *et al* [38] reported some contradicting results given that it did not find any cross-reactivity between crickets/locusts and prawn/mite. However, this may be due to this study being performed with a subject that was only sensitised to the insects. Furthermore, the patient did not have sIgE to tropomyosin and on Immunoblot it did not present any IgE-binding bands with tropomyosin molecular mass, which might explain the lack of cross-reactivity. This study also raises the question if primary sensitisation to insects can lead to cross-reactivity with crustaceans. In addition to these studies (which were performed with crustacean/HDM allergic patients), three articles [43-45] have been published using sera from silkworm-allergic patients and have characterized AK, chitinase, paramyosin and a heat-stable 27 kDa-glycoprotein as important silkworm allergens. These studies highlight the importance of using sera from insect-allergic patients in the identification of the allergens responsible for allergic reactions to insects, as allergens responsible for cross-reactivity may be different from allergens responsible for primary sensitisation.

The clinical relevance of cross reactivity between insects and crustaceans is suggested by two cases [52, 54] where subjects with food allergy to shellfish also developed food allergy following consumption of cicadas [52] and vegetable worms [54]. Only one study [36] has performed a DBPCFC with shrimp-allergic and shrimp/HDM-allergic patients, and the results showed that cross-reactivity/co-sensitisation between crustaceans and yellow mealworm is clinically relevant, as most patients (87 %) developed objective symptoms after consuming this insect. This high percentage (87 %) of shrimp-allergic patients with clinical symptoms to ingestion of yellow mealworm is somewhat surprising because for different species of shellfish the risk reported was of 75 % [69]. However, the relatively small sample size hampers the generalization of the findings of this study and more studies with DBPCFC are necessary to confirm these initial results. Despite articles reporting IgE-binding

from HDM-allergic subjects to edible insects [41] and allergens being identified in silkworm [45] (chitinase and paramyosin) that have high sequence homology with HDM allergens, food challenges are necessary to determine if cross-reactivity/co-sensitisation has any clinical significance [26]. IgE-binding or IgE cross-reactivity does not necessarily mean that an allergic reaction will occur – as seen in the cases between related foods in the legume family [70]. Assessing the clinical significance of cross-reactivity/co-sensitisation between insects and HDM is particularly important because if HDM-sensitive subjects develop food allergy to insects, the use of insects as food could be jeopardized due to the high rate of HDM-sensitised subjects in the world.

Taking into account that in the vast majority of cases the allergic reaction occurred after consuming the insect for the first time, it is possible to hypothesize that these latter subjects had already been sensitized to insects or had been sensitized to either crustaceans or HDM. In fact, it is known that, due to cross-reactivity between shrimp and HDM, it is possible to become co-sensitized to each one of them without having been exposed to them [71, 72]. Cross-reactivity between food allergens and other allergens is very common as seen in the cases of snails and mites [73-75]. On the other hand, in 3 cases, food allergy to yellow mealworm occurred in subjects who were constantly exposed and became sensitized to yellow mealworm [46, 47]. The danger of insect-rearing workers becoming hypersensitive to insects has been established [19-21], and, in spite of the differences between inhalant and food allergy (food sensitivity occurs at a much higher dose), one should consider the hypothesis that a constant exposure to insects might lead to both inhalant and food allergy. There are reports of similar cases where subjects became sensitised to the food through inhalation and later developed a food allergy. These cases have been reported in lupine seed flour, egg, sunflower seeds [76] and garlic [77].

One major limitation of studying the allergic risks of consuming insects concerns the lack of information regarding the cases of allergic reactions. This limitation partly mirrors the fact that entomophagy is mainly widespread in Africa and Asia. As a result, a substantial number of reactions

might go unnoticed or might only be reported in local journals. To our knowledge, this is the first systematic review encompassing case reports and case series of food allergy to insects, as well as assessing the possibility of cross-reactivity with other allergens. Regarding the insect species causing the allergic reactions, silkworm pupae, grasshoppers and locusts were the ones most frequently identified. However, that does not necessarily mean that these are the species most likely to cause allergic reactions, as the type and species consumed vary greatly through regions and as previously mentioned, many reactions might go unnoticed. For instance silkworm pupae are widely consumed in China and it is estimated that each year over 1000 patients suffer from anaphylactic reaction after consumption, with 50 needing to receive emergency room treatment for severe anaphylactic reactions [55]. Another limitation in some of these studies concern the lack of important information to understand the context of reactions, particularly the allergic history of the subject or sensitization to other allergens (e.g. HDM or shellfish) was lacking in several articles. Only one article [59] studied the frequency of food allergy to insects among insect-eaters, reporting an apparent low prevalence (7.6 %) of allergic reactions of which none corresponded to a case of severe anaphylaxis or fatality. Moreover, such prevalence could even be inflated given that the cases of allergy were self-reported and could have been caused by stings or venom from the insects. Despite reports that insect consumption was responsible for 17,3% [56], 19,4% [58] or 4,2% [57] of food-induced anaphylaxis in China and Thailand respectively, prevalence of allergy to insect consumption does not seem to be high, since several studies performed in Asia (including China and Thailand) that assess the prevalence of food allergy do not even mention insects as important causative agents of food allergy [78, 79]. It is also noteworthy to mention that for the future, more studies dealing with the prevalence of insect food allergy should be performed, particularly evaluating whether the patients have other food allergies or if they are sensitized to either crustaceans or HDM.

In conclusion, the articles reviewed here seem to confirm the allergic risk for crustacean-allergic subjects to consumption of insects while the clinical significance for the cross-reactivity between

HDM and edible insects needs to be established. There are also signs that subjects who are constantly exposed to insects (like insect-rearing workers) may develop food allergy, which may be a cause of concern with the prospect of increasing insect-rearing units for mass production of insects for food and feed. Although tropomyosin and AK seem to be the major cross-reacting allergens, their clinical significance needs to be assessed and their role should be further established through inhibition studies.

Author contributions:

José Carlos Ribeiro has conducted the bibliographical research and drafted the manuscript, Luís M. Cunha has supervised the study, designing the bibliographical research and the manuscript structure and revising the final document. Bernardo Sousa-Pinto has contributed to the drafting and revision of the manuscript. João Fonseca has contributed to the design of the study and revision of the final document.

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Conflict of interest:

The authors declare there are no conflicts of interest.

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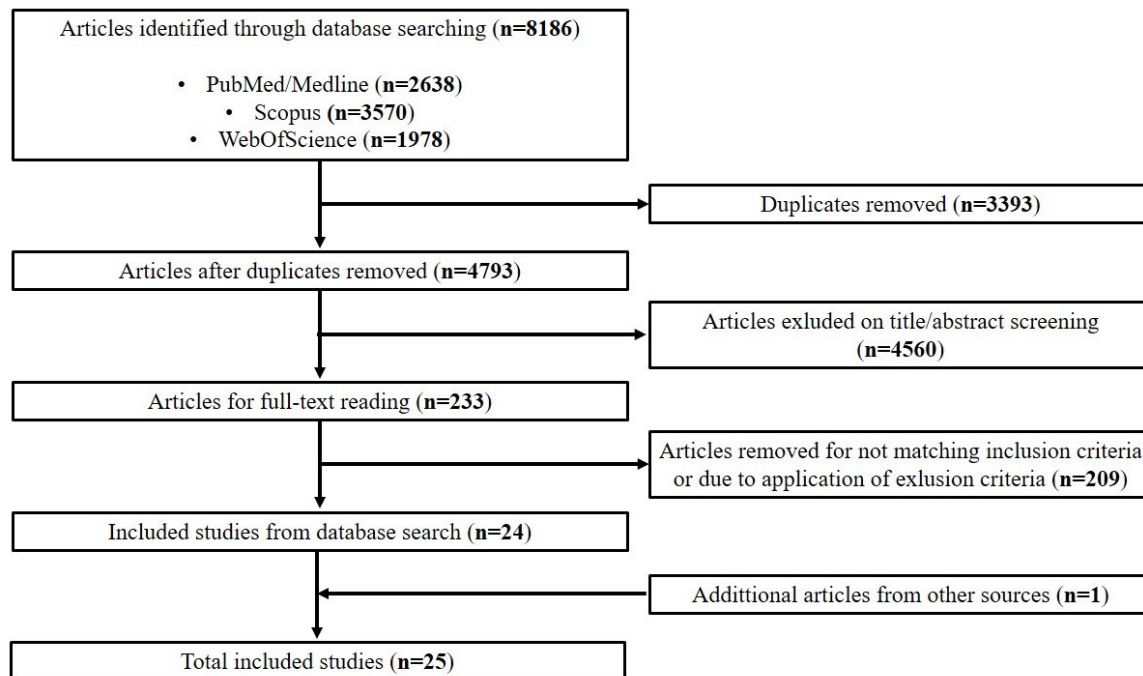
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Figure captions

Figure 1. Flow chart of study inclusion/exclusion



Graphical Abstract

- A systematic review aiming to analyse current data available regarding the allergic risks of consuming edible insects was performed.
- Consumers allergic to crustaceans should avoid edible insects due to risk of allergic reaction.
- Workers at insect farms should be monitored for the development of both inhalant and food allergy caused by those edible insects reared at the farms.

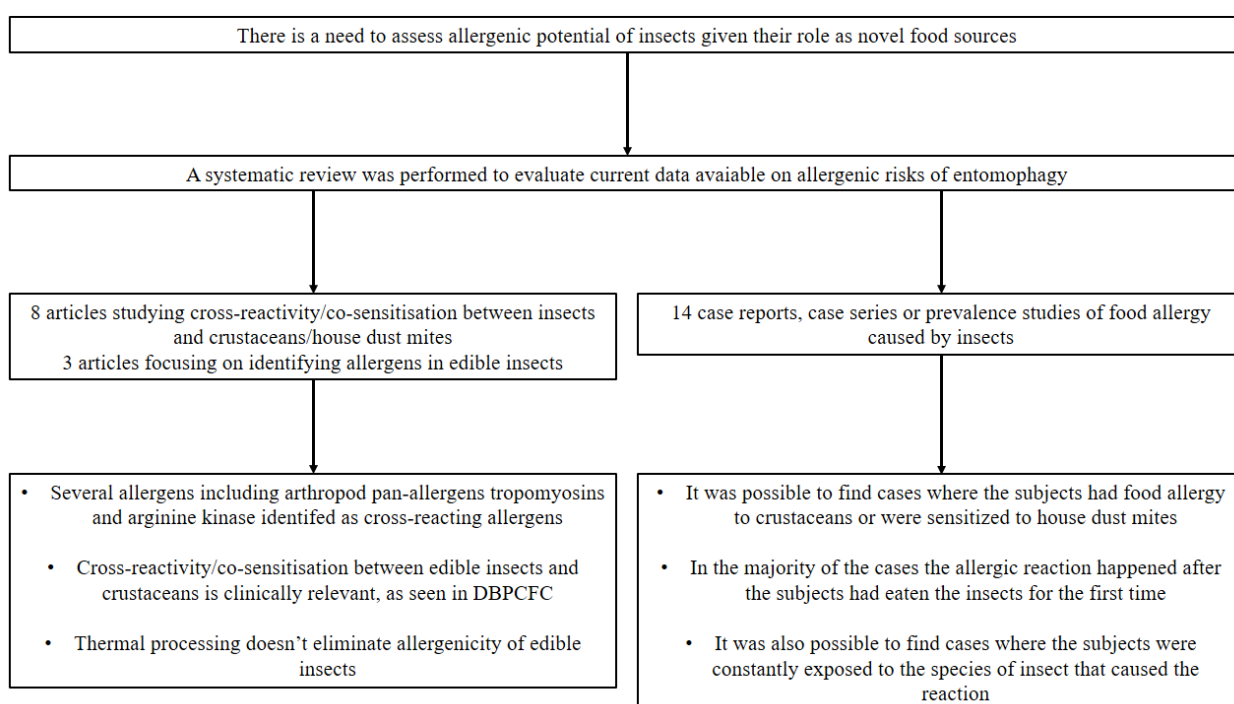


Table 1. List of articles studying cross-reactivity/co- sensitisation between edible insects and crustaceans/HDM and detection of allergens in edible insects.

Edible insect species studied	Sera from patients allergic to	IgE-binding proteins	Methodological characteristics	Article
Yellow mealworm (<i>Tenebrio molitor</i>)	Crustaceans/HDM Der p 10 (n=7)	Tropomyosin, AK (major)	Immunoblot; Immunoprecipitation; BAT; Determination of allergic potential with Allermatch; Nano LC-MS/MS	Verhoeckx, 2014 [42]
		α -tubulin, β -tubulin, fructose-biphosphate aldolase, myosin light chain (minor)		
Yellow mealworm (<i>Tenebrio molitor</i>)	Shrimp (n=3 for immunoblot; n=15 for SPT; n=12 for BAT)	Tropomyosin AK	Thermal processing of mealworm extracts; SDS-PAGE; LC-MS/MS; Immunoblot; BAT; SPT	Broekman, 2015 [35]
Yellow mealworm (<i>Tenebrio molitor</i>)	Shrimp (n=15)	Tropomyosin AK	DBPCFC; SPT; ImmunoCAP; BAT; Immunoblot	Broekman, 2016 [36]
Yellow mealworm (<i>Tenebrio molitor</i>)	Crustaceans (n=8 for dot-blot and n=6 for immunoblot)	Tropomyosin, actin (Crustaceans)	Processing (boiling, frying or lyophilising) and <i>in vitro digestion</i> of larvae extracts; Immunoblot; Dot-blot; MALDI-MS/MS; Determination of allergic potential with Allermatch	Van Broekhoven, 2016 [41]
Lesser mealworm (<i>Alphitobius</i>)	HDM (n=11 for dot-blot and n=7)	Paramyosin, α -amylase, HEX1B, heavy		

<i>diaperinus</i>)	for immunoblot)	chain muscle myosin (HDM)		
Super mealworm (<i>Zophobas atratus</i>)				
Field cricket (<i>Gryllus bimaculatus</i>)	Prawn (n=16)	AK (major)	SDS-PAGE; Immunoblot; LC-MS/MS	Srinroch, 2015 [40]
		HEX1B (minor)		
Bombay locust (<i>Patanga succinta</i>)	Prawn (n=16)	AK (raw)	Thermal processing of Bombay locust extracts; SDS-PAGE; Immunoblot; Glycoprotein Staining; LC-MS/MS	Phiriyangkul, 2015 [39]
		HEX1B, enolase (raw and fried)		
		GADPH, pyruvate kinase (fried)		
Grasshopper (<i>Mecopoda elongata</i>)	Shrimp (n=9)	Tropomyosin	Immunoblot; Inhibition immunoblotting	Leung, 1996 [37]
Field cricket (<i>Gryllus bimaculatus</i> ; <i>Gryllus campestris</i>)	Field cricket (<i>Gryllus bimaculatus</i> ; <i>Gryllus campestris</i>)		EAST Inhibition with prawn and mite <i>Dermatophagoides pteronyssinus</i> .	Linares, 2008 [38]
House cricket (<i>Acheta domesticus</i>)	House cricket (<i>Acheta domesticus</i>)			
Silkworm (<i>Bombyx mori</i>) larva	Silkworm (<i>Bombyx mori</i>) larva (n=10)	AK	Immunoblot; Immunoblot Inhibition Assay; ELISA; ELISA	Liu, 2009 [44]

			Inhibition Assay	
Silkworm (<i>Bombyx mori</i>) pupae	Silkworm (<i>Bombyx mori</i>) pupa (n=15)	27-kDa Glycoprotein	Boiling of protein extract; Immunoblot; Proteomic analysis; Inhibition immunoblotting; ELISA; ELISA inhibition	Jeong, 2015 [43]
Silkworm (<i>Bombyx mori</i>) pupae	Silkworm (<i>Bombyx mori</i>) pupae (n=4)	Chitinase	2-DE; Western blot; Immunoblot; MALDI-TOF-MS; Sequence analysis	Zhao, 2015 [45]
		Paramyosin		

Table 2. List of case reports and case series of food allergy to insects organized by article with information regarding species, clinical symptoms evoked to ingestion of the insect and other characteristics of the subjects.

Article	Age/Sex/Nationality	Species	Clinical symptoms	Personal history	Other characteristics
Freye,1996 [47]	NA/NA/American	Yellow mealworm (<i>Tenebrio molitor</i>)	U, D and P (throat, tongue and palm of hands)	Regularly exposed to superworm, yellow mealworm and german cockroach; Hypersensitive to inhalation of these species (bronchospasm, conjunctivitis and rhinitis)	Positive SPT and sIgE to superworm, mealworm and cockroach; positive intradermal skin testing to common indoor and outdoor allergens.
Broekman, 2015 [46]	28/M/Dutch	Yellow mealworm (<i>Tenebrio molitor</i>)	OA,U	Domestic breeder of yellow mealworm	Positive DBPCFC to mealworm; negative oral challenge to shrimp; sensitised (SPT and ImmunoCAP) to mealworm
Broekman, 2015 [46]	32/M/Dutch	Yellow mealworm (<i>Tenebrio molitor</i>)	OA,U	Domestic breeder of yellow mealworm; Allergic respiratory diseases to mealworm, HDM and birch pollen.	Positive DBPCFC to mealworm; negative oral challenge to shrimp; sensitised (SPT, ImmunoCAP AND ImmunoCAP ISAC) to mealworm and HDM
Ji, 2008 [55]	37/M/French (visiting China)	Silkworm (<i>Bombyx mori</i>) pupa	I (mouth and face), N, S (face) , DB, H	History of allergic rhinitis; first time consuming silkworm pupa	
Ji, 2008 [55]	21/M/Chinese	Silkworm (<i>Bombyx mori</i>) pupa	P,U,S,H,F,UC	No history of previous allergic shock; first time consuming silkworm pupa	
Ji, 2008 [55]	19/M/Chinese	Silkworm (<i>Bombyx mori</i>) pupa	U,S,HA,H,AP,V,DY	No history of previous allergic shock; first time consuming silkworm pupa	

	37/F/Chinese				
	54/F/Chinese				
Ji, 2008 [55]	M/20/Chinese	Silkworm (<i>Bombyx mori</i>) pupa	P,U,S,H,F,N,UC	No history of previous allergic shock; first time consuming silkworm pupa	
Ji, 2008 [55]	5 males: 9-46	Silkworm (<i>Bombyx mori</i>) pupa	P,U,S,A,AP,V,N,D	No history of previous allergic shock; no history of previous history; first time consuming silkworm pupa	
	3 females: 9-46				
Gautreau, 2016 [48]	M/44/Nepalese (living in U.S.A)	Silkworm (<i>Bombyx mori</i>) pupa	U,FL,DS	First time consuming silkworm pupa	
Gautreau, 2016 [48]	M/18/Nepalese (living in U.S.A)	Silkworm (<i>Bombyx mori</i>) pupa	FL,E (face), U	First time consuming silkworm pupa	
Choi, 2010 [54]	F/22/Korean	Vegetable worm (<i>Cordyceps sinensis</i>)	R,C,A	History of allergic rhinitis	Similar symptoms to consumption of silkworm pupa;
Choi, 2010 [54]	M/40/Korean	Vegetable worm (<i>Cordyceps sinensis</i>)	U	History of allergic rhinitis	Similar symptoms to consumption of silkworm pupa;
Choi, 2010 [54]	F/33/Korean	Vegetable worm (<i>Cordyceps sinensis</i>)	U	History of contact urticaria	Similar symptoms to consumption of silkworm pupa;
Choi, 2010 [54]	M/39/Korean	Vegetable worm (<i>Cordyceps sinensis</i>)	P	History of allergic rhinitis and bronchial asthma	Similar symptoms to consumption of silkworm pupa;
Choi, 2010 [54]	F/24/Korean	Vegetable worm (<i>Cordyceps sinensis</i>)	U	History of allergic rhinitis and food allergy to seafood	Similar symptoms to consumption of silkworm pupa;
Kung, 2013 [50]	M/39/Batswana	Mopane worm (<i>Imbrasia belina</i>)	I (throat and palatal), U	History of allergic conjunctivitis	Positive SPT to dust mites and mopane worm.
Kung, 2011 [49]	M/15/Batswana	Mopane worm (<i>Imbrasia belina</i>)	DY, P (palatal), U, S (tongue and lips), HA	History of allergic rhinitis and infantile	Positive SPT to trees, grass, dust mites, weed, cockroach and

				eczema.	mopane worm.
Okezie, 2010 [51]	F/36/Batswana	Mopane worm (<i>Imbrasia belina</i>)	S (body and face), I (generalized), N, RA, H	Had eaten mopane worm all her life without problem.	
Yew, 2012 [53]	M/46/Chinese	Sago worms (<i>Rhynchophorus ferrugineus</i>)	I (face, arms and body), DB, Takotsubo Cardiomyopathy	First time eating sago worms	
Piatt, 2005 [52]	M/45/American	Cicadas	U	Food allergy to shellfish	
	U	(associated with Brood X cicada invasion in the USA, where species of <i>Magicada septendecim</i> , <i>Magicada cassini</i> and <i>Magicada septendecula</i> were identified)			

F- Female, M- Male; A – Angioedema, AP – Abdominal Pain, C – Conjunctivitis D – Diarrhea, DB – Difficulty in breathing, DS – Dry Skin, DY – Dyspnoea, E – Edema, F – Fainting, FL – Flushed, H – Hypotension, HA - Headache I – Itchiness, N – Nausea, OA – Oral Allergy, P – Pruritus, R – Rhinitis, RA - Rash S – Swelling, V – Vomiting, U – Urticaria, UC - Unconsciousness