We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800 Open access books available 122,000

135M



Our authors are among the

TOP 1%





WEB OF SCIENCE

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us? Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected. For more information visit www.intechopen.com



Allergy to Edible Insects: A Computational Identification of the IgE-Binding Cross-Reacting Allergen Repertoire of Edible Insects

Pierre Rougé and Annick Barre

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/68124

Abstract

Allergic manifestations to the ingestion of edible insects have been reported, especially in countries where edible insects are traditionally consumed. However, to date, allergens of edible insects have been poorly investigated. The AllergenOnline server was used for assessing the allergenic character of the putative IgE-binding crossreactive allergens from the consumed yellow mealworm, silkworm, house fly maggot, migratory locust, house cricket, greater wax moth, black soldier fly, American grasshopper and Indian mealmoth. Positive hits correspond to allergens exhibiting >35% identity over an 80-residue sliding window and 100% identity over an 8-residue sliding window, respectively. Most of the hits consist of allergens from arthropods such as dust mites, crustaceans and insects, and more rarely, of allergens from mollusks, nematodes, and fungi. All the identified allergens share conserved amino acid sequences and three-dimensional structures. Accordingly, the allergens of edible insects form clusters closely related to crustacean, mollusk and nematode clusters into the phylogenetic trees built up from the sequence alignments. Our computational investigations suggest edible insects possess a large repertoire of IgE-binding allergens they share with phylogenetically related groups of arthropods, mollusks, and nematodes. These cross-reacting allergens are susceptible to trigger allergic reactions in individuals previously sensitized to shellfish or mollusks.

Keywords: allergen repertoire, edible insects, shrimps, dust mites, mollusks, IgE-binding cross-reactivity



© 2017 The Author(s). Licensee InTech. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. (cc) BY

1. Introduction

The rapidly expanding world population, which is estimated to reach 9 billion people on 2040, underlines the urgent need to develop new sources of food proteins as a complement for the traditionally consumed proteins of plant and animal origin [1–3]. Among the new sources of food and feed proteins, insect proteins appear as a valuable candidate with respect to their good nutritional value for humans and animals [4] and their ability to be produced at a very large industrial scale [5]. However, insect proteins have to be checked for food and feed security before the launching of any large-scale production [6-9]. In this respect, both the chemical (heavy metal and pesticide contamination) and biological safeties including the potential parasitic microbial and parasitic load, and the potential allergenicity, should be evaluated. Depending on the forthcoming predictable introduction of edible insect proteins in both the human and cattle diets, the potential allergic risk associated to the consumption of edible insects has been stressed out, due to the occurrence in insects of pan-allergens common to arthropods, mollusks, and nematodes [8–10]. To date, however, our knowledge on the diversity of insect allergens remains too limited to properly address the potential allergic risk associated to entomophagy, especially for people living in European countries where insect consumption is not a part of their eating habits. In the present chapter, we report the results of a bioinformatic approach aimed at filling the gaps in our existing knowledge about the variety of allergens occurring in some edible insect species.

2. Assessing the complexity of the IgE-binding allergen repertoire of edible insects

A bioinformatic approach based on the AllergenOnline server (http://allergenonline.org) was used for assessing the allergenic character of the putative IgE-binding cross-reactive allergens of some edible insects. Analysis of the available amino acid sequences of putative allergens from yellow mealworm (*Tenebrio molitor*), silkworm (*Bombyx mori*), house fly maggot (*Musca domestica*), migratory locust (*Locusta migratoria*), house cricket (*Acheta domesticus*), grater wax moth (*Galleria mellonella*), black soldier fly (*Hermetia illucens*), American grasshopper (*Schistocerca americana*), and Indian mealmoth (*Plodia interpunctella*) was performed using two large (80 amino acid residues) and restricted (8 amino acid residues) sliding windows, respectively. Positive hits from the AllergenOnline data bank correspond to allergens exhibiting >35% identity over an 80-residue window and 100% identity over an 8-residue window, respectively. The FASTA search algorithm (FASTA 35.04, 2009) was used with the standard E-value cutoff of 1. For each assayed putative insect allergen, the number of positive hits for both the global (80mer window) and the local (8mer window) identities is indicated in **Table 1**.

Allergy to Edible Insects: A Computational Identification of the IgE-Binding Cross-Reacting... 73 http://dx.doi.org/10.5772/68124

Insect	Putative allergen	(No. hits 80mer)	(No. hits 8mer)
Tenebrio molitor	Alpha-amylase	6	41
	Chitinase	2	0
	Cockroach allergen	10	0
	Glutathione S-transferase	3	57
	HSP 70	7	389
	Hexamerin	9	37
	Serine protease	11	0
	Triosephosphate isomerase	4	132
Bombyx mori	Actin	0	0
	Alpha-amylase	4	43
	Arginine kinase	14	1431
	Chitinase	2	3
	Glutathione S-transferase	4	24
	HSP 70	7	218
	Hemocyanin	9	12
	Sarcoplasmic Ca-binding protein	4	6
	Serine protease	3	0
	Triosephosphate isomerase	4	107
	Tropomyosin	75	866
	Troponin C	12	115
	Trypsin	10	0
	Beta-tubulin	0	0
Iusca domestica	Actin	0	0
	Alpha-amylase	6	25
	Arginine kinase	14	1045
	Chitinase	2	0
	Glutathione S-transferase	3	9
	HSP 70	7	633
	Hemocyanin	9	3
	Sarcoplasmic Ca-binding protein	0	0
	Serine protease	14	6
	Triosephosphate isomerase	4	106
	Tropomyosin	76	4547
	Troponin C	10	19
	Trypsin	15	19
	Beta-tubulin	0	0

Insect	Putative allergen	(No. hits 80mer)	(No. hits 8mer)
Locusta migratoria	Actin	0	0
	Arginine kinase	14	1329
	Chitinase	2	0
	Glutathione S-transferase	3	4
	HSP 70	8	602
	Hexamerin	9	0
	Serine protease	16	13
	Tropomyosin	76	5455
	Trypsin	16	13
	Beta-tubulin	0	0
Acheta domesticus	Triosephosphate isomerase	4	27
Galleria mellonella	Glutathione S-transferase	3	22
	Hemocyanin	9	23
	Trypsin	16	12
Hermetia illucens	Alpha-amylase	6	56
	Serine protease	16	19
	Trypsin	16	57
Schisto americana	Arginine kinase	14	1383

Table 1. Global (80mer) and local (8mer) identities found for the putative insect allergens.

3. IgE-binding allergens of edible insects belong to conserved protein families

Bioinformatic investigations using a sliding window of 80 amino acids resulted in a large number of positive hits for the putative allergen proteins of all the insect species, with the exception of actin, sarcoplasmic Ca-binding protein (SCBP), and β -tubulin (**Table 1**). However, some of the global identities do not necessarily coincide with local identities, since no hit was found with a more restricted sliding window of eight amino acid residues. Both global and local identities were found with the thioredoxin allergen of silkworm, house fly maggot, and the Indian mealmoth (*P. interpunctella*).

Most of the hits found with the 80mer and 8mer windows consist of allergens from arthropods such as dust mites, crustaceans, and insects and, more rarely, of allergens from mollusks, nematodes, and fungi (*Alternaria alternata, Aspergillus oryzae, Aspergillus fumigatus, Cladosporium herbaceum, Malassezia sympodialis*) (**Table 2**). For a limited number of putative insect allergens like the widely distributed heat shock protein HSP 70, serine protease, trypsin, triosephosphate isomerase (TPI), and thioredoxin, hit allergens of plant (the blue cypress Cupressus arizonica, the maize *Zea mays,* the wheat *Triticum aestivum,* the common ragweed *Ambrosia artemisiifolia,* the olive tree *Olea europaea*) and animal (the Mozambique tilapia *Oreochromis mossambicus*, the dog *Canis familiaris*) origin were identified. Obviously, these allergens consist of ubiquitous pan-allergens that occur in so distantly phylogenetically related or phylogenetically unrelated organisms.

Protein family	Insects	Dust mites	Crustaceans	Mollusks/Nematodes
Actin		(1)	-	_
Alpha-amylase	Bla g 11	Blo t 4		
	Per a 11	Der f 4		
	(+2)	Der p 4		
		Eur m 4 (+2)		
Arginine kinase	Bomb m 1	Der f 20	Cra c 2	(4)
	Per a 9	Der p 20 (+3)	Lit v 2	
	Plo i 1 (+5)		Pen m 2 (+23)	
Chitinase	Per a 12 (+1)	Der f 15 (+5)	-	-
Glutathione	Bla g 5 (+1)	Blo t 8	-	-
S-transferase		Der f 8		Asc l 13 (N)
		Der p 8 (+6)		Asc s 13 (N)
HSP 70 (heat shock protein)	Aed a 8 (+2)	Der f 28	-	-
		Tyr p 28		
Hemocyanin	Bla g 3	-	(1)	-
	Per a 3			
Hexamerin	(6)	_	-	-
Myosin	Bla g 8 (+1)	Der f 26	Art fr 5	-
			Cra c 5	-
			Hom a 3	
			Lit v 3	
			Pen m 3 (+1)	
Sarcoplasmic Ca-binding protein	Aed a 5 (+2)		Cra c 4	
			Eri s 4	
			Lit v 4	
			Mac r 4	
			Pen m 4	
			Pon l 4 (+24)	
Serine protease	Api m 7	Der f 6	_	_
	Bom t 4	Der p 6		
	Per a 10	Eur m 1 (+12)		

Protein family	Insects	Dust mites	Crustaceans	Mollusks/Nematodes
Triosephosphate isomerase	Pol d 4			
	Pol e 4 (+14)			
Tropomyosin	(2)	Der f 25	Arc s 8, Cra c 8	_
	Aed a 10	Blo t 10	Cha f 1	Ani s 3 (N)
	Bla g 7	Cho a 10	Cra c 1	Asc 1 3 (N)
	Chi k 10	Der f 10	Hom a 1	Hel as 1 (+50)
	Lep s 1	Der p 10	Lit v 1	
	Per a 7 (+29)	Lep d 10	Mac r 1	
		Tyr p 10 (+11)	Mel l 1	
			Met e 1	
			Pan s 1	
			Pen a 1	
			Pen m 1	
			Por p 1 (+54)	
Troponin C	Bla g 6, Per a 6	Tyr p 34	Cra c 6	
			Hom a 6	(1 N)
			Pen m 6 (+2)	
Trypsin	(4)	Blot 3	-	_
		Der f 3		
		Der p 3		
		Eur m 3		
		Tyr p 3 (+3)		
Alpha-tubulin	_	Der f 33 (+2)	_	_

The Internaional Union of Immunological Societies (IUIS) nomenclature (the three first initial of the genus name, followed by a number indicating the ranking of discover, e.g., **Lit v 2** for the shrimp *Litopenaeus vannamei* **2** allergen) was used. Allergens referenced by IUIS (2016) are indicated; numbers into brackets represent other allergens nonreferenced by IUIS but included into the AllergenOnline data bank.

Table 2. Nomenclature of the IgE-binding allergens belonging to the main allergenic protein families identified in insects, dust mites, crustaceans, mollusks, and nematodes (N).

All the insect allergens identified so far consist of proteins which belong to families of highly conserved proteins, namely, muscle proteins such as tropomyosin, myosin, and the sarcoplasmic Ca-binding protein and enzymes such as α -amylase, chitinase, glutathione S-transferase (GST), arginine kinase, serine protease, and trypsin. Most of these proteins have been already identified as allergens of both the German (*Blattella germanica*) and American cockroach (*Periplaneta americana*) (http://Allergome.org). According to the high degree of conservation, all of these allergens are distributed among phylogenetically related clusters in

the phylogenetic trees built up from their amino acid sequence alignments. As an example, **Figure 1** illustrates the phylogenetic tree built up from the glutathione S-transferase multiple alignment. Very similar trees were built up from the multiple alignments of other enzyme allergens from edible insects, crustaceans, mollusks, and nematodes (results not shown), except for the tropomyosin tree, in which insect tropomyosins cluster in two separate groups

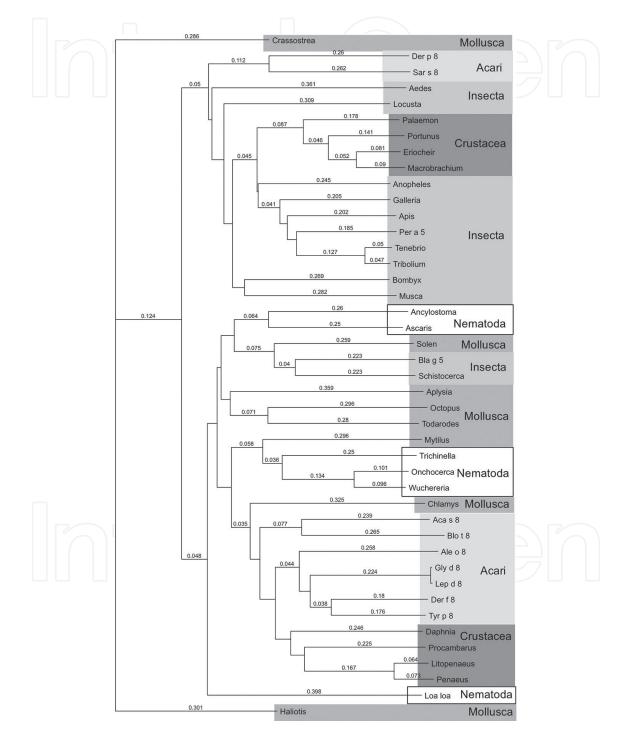


Figure 1. Phylogenetic tree built up from the amino acid sequence alignment of glutathione S-transferase allergens of dust mites, insects, crustaceans, mollusks, and nematodes. Clusters corresponding to dust mites, insects, crustaceans, mollusks, and nematodes are differently shaded.

that are differently phylogenetically related to the dust mite tropomyosin cluster [11]. This discrepancy observed in the distribution of insect tropomyosins is consistent with the fact that some of the dust mite tropomyosin-reactive patient sera strongly interacted with a tropomyosin-containing mealworm extract in western blot experiments, whereas other dust mite tropomyosin-reactive patient sera at all [11].

3.1. Muscle proteins

The muscle proteins tropomyosin, myosin, and sarcoplasmic Ca-binding protein (SCBP) have been identified as major allergens of edible insects. Especially, tropomyosin appears as a major pan-allergen largely distributed among dust mites, insects, crustaceans, mollusks, and nematodes [12-16]. Major allergens of dust mites, e.g., Aca s 10 from Acarus siro, Blo t 10 from Blomia tropicalis, Der f 10 and Der p 10 from Dermatophagoides farinae and Dermatophagoides pteronyssinus, Gly d 10 from Glycyphagus destructor, Ixo sc 10 from the shoulder tick Ixodes scapularis, and Tyr p 10 from Tyrophagus putrescentiae, consist of tropomyosins (Allergome. org). Many other tropomyosins consist of the major allergens of insects, e.g., Bla g 7 and Per a 7 from the cockroaches *B. germanica* and *P. americana*, Bomb m 7 from the edible pupa of B. mori, Aed a 7, and Cul q 7 from the mosquitos Aedes aegypti and Culex quinquefasciatus, and Chi k 10 from the chironomid Chironomus kiiensis, Dro m 7 from the fruit fly Drosophila melanogaster, Glo m 7 from the tsetse fly Glossina morsitans, and Loc m 7 from the edible locust L. migratoria (Allergome.org). Many crustacean species also contain tropomyosin as a major muscle allergen, e.g., Cra c 1 from the common shrimp Crangon crangon, Eri s 1 from the crab Eriocheir sinensis, Hom a 1 from the American lobster Homarus americanus, Lit v 1 and Pen m 1 from the prawns Litopenaeus vannamei and Penaeus monodon, Nep n 1 from the scampi Nephrops norvegicus, etc. (Allergome.org). Tropomyosin also occurs as a major allergen in various mollusks like Cra g 1 from the oyster Crassostrea gigas, Hel a from the snail Helix aspersa, Hal a 1 from the abalone Haliotis asinina, Lol b 1 from the spear squid Loligo bleekeri, Myt e 1 from the blue mussel Mytilus edulis, Oct v 1 from Octopus vulgaris, Por t 1 from the Japanese blue crab Portunus trituberculatus, and Sep of 1 from the common cuttlefish Sepia officinalis (Allergome.org). Finally, tropomyosin also consists of the major allergen Ani s 3 of the nematode *Anisakis simplex* (http://Allergome.org).

Other muscle protein allergens like troponin and the sarcoplasmic Ca-binding protein (SCBP) also provide a number of allergens like the troponins Tyr p 24 from the dust mite *T. putrescentiae*, Bla g 6 and Per a 6 from the cockroaches *B. germanica* and *P. americana*, Cra c 6 and Pen m 6 from the shrimps *C. crangon* and *P. monodon*, Hom a 6 from the American lobster *H. americanus*, and the troponin of the nematode *A. simplex* (Allergome.org). The sarcoplasmic Ca-binding protein also occurs as an allergen in insects (Aed a 4 and Cul q 4 from the mosquitos *Aedes aegypti* and *C. quinquefasciatus*) and crustaceans (Cra c 4 from *C. crangon*, Eri s 4 from the Chinese crab *E. sinensis*, Hom a 4 from the lobster *H. americanus*, Mac r 4 from the giant freshwater prawn *Macrobrachium rosenbergii*, Pen m 4 from *P. monodon*, Scy pa 4 from the green mud crab *Scylla paramamosain*) (Allergome.org). To date, no SCBP has been identified as an allergen in mollusks and nematodes.

All of these muscle protein allergens display a rather high resistance to both the proteolysis and heat denaturation, as exemplified by the experiments performed on the tropomyosin of different species of mealworm [17] and the oyster *Crassostrea gigas* [18].

3.2. Enzymes

A number of enzymes including hydrolases like α -amylase, chitinase, serine protease, and trypsin and metabolic enzymes like arginine kinase (AK), glutathione S-transferase (GST), and triosephosphate isomerase (TPI) have been identified as cross-reacting allergens of edible insects [11, 19–23].

Arginine kinase has been previously identified as a pan-allergen widely distributed in various insects such as the yellow mealworm (*T. molitor*) [20], the field cricket (*Gryllus bimaculatus*) [23], and the house cricket (*A. domesticus*) [11]; shrimps like the black tiger prawn (*P. monodon*) and the king prawn (*Penaeus latisulcatus*) [24]; the giant freshwater prawn (*M. rosenbergii*) [23, 25]; and crabs like the blue swimming crab (*Portunus pelagicus*) [26] and the red crab (*c*) [27]. Arginine kinases consist of the major allergens Bla g 9 of the German cockroach (*B. germanica*) and Per a 9 of the American cockroach (*P. americana*) (Allergome.org). Many other allergens of dust mites like Blo t 20 of *B. tropicalis*, Der f 20 of *D. farinae*, Der p 20 of *D. pteronyssinus*, and Gly d 20 of *G. destructor* also consist of arginine kinases (Allergome.org). The list of arginine kinase allergens of crustaceans is also consistent (http://Allergome.org).

Alpha-amylase, a hydrolase of paramount importance for the digestion of starch by herbivorous and omnivorous organisms, occurs as an allergens in dust mites (Aca s 4 of *A. siro*, Blo t 4 of *B. tropicalis*, Der p 4 of *D. pteronyssinus*, Eur m 4 of *Euroglyphus maynei*, Tyr p 4 of *T. putrescentiae*) and insects (Sim v 3 and Sim v 4 of the striped black fly *Simulia vittata*, Bla g 11 and Per a 11 of the cockroaches *B. germanica* and *P. americana*) (http://Allergome.org).

Other metabolic enzymes like the glutathione S-transferase GST (Aca s 8 of *A. siro,* Blo t 8 of *B. tropicalis,* Der f 8 and Der p 8 of *D. farinae* and *D. pteronyssinus,* Tyr p 8 of *Tyroglyphus putrescentiae,* Bla g 5 and Per a 5 of *B. germanica* and *P. americana*), chitinase (Blo t 15 of *B. tropicalis,* Der f 15 and Der p 15 of *D. farinae* and *D. pteronyssinus,* and Per a 12 of the cockroach *P. americana*), and triosephosphate isomerase TPI (Der f 25 of *D. farinae,* Bla g TPI of the cockroach *B. germanica,* For t TPI of the biting midge *Forcipomyia taiwana,* and Cra c 8 of the shrimp *C. crangon*) also consist of allergens essentially in dust mites and insects (Allergome.org). However, they seem to be less widely distributed in arthropods than other enzymes like arginine kinase.

3.3. Other proteins

Other proteins involved in metabolic pathways (HSP70, thioredoxin) or displaying structural (tubulin) or physiological (hemocyanin and hexamerin) functions also occur as minor allergens in edible insects (**Table 2**). The hemolymph proteins hemocyanin and hexamerin both consist of homotetrameric proteins of high molecular mass, which share very conserved amino acid sequences and three-dimensional conformations. Hexamerin is widely distributed

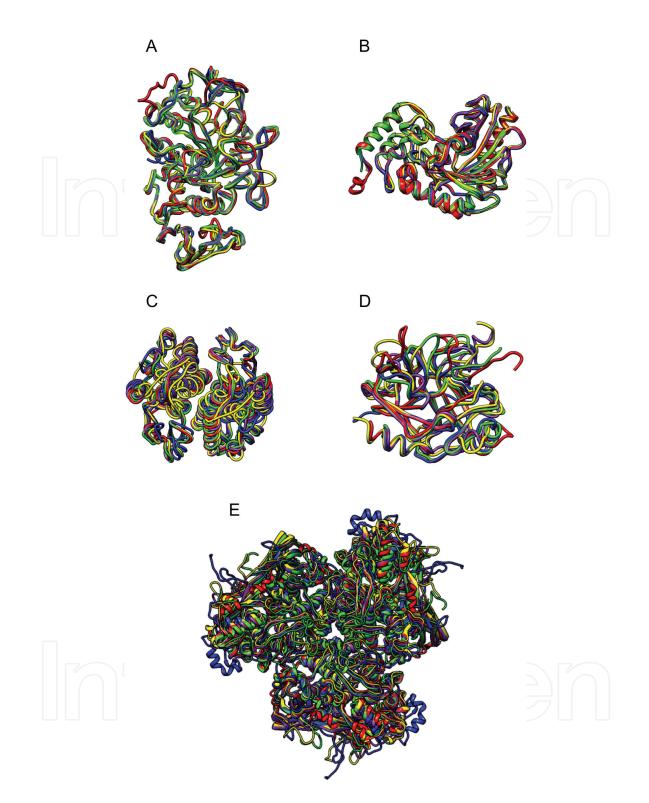


Figure 2. (A) Superimposition of the three-dimensional ribbon diagrams of α-amylase allergens of *Bombyx mori*, *Hermetia illucens, Musca domestica* and *Apis mellifera*. (B) Superimposition of the three- dimensional ribbon diagrams of arginine kinase allergens of *Bombyx mori*, *Locusta migratoria, Musca domestica, Apis mellifera* and *Schistocerca americana*. (C) Superimposition of the three-dimensional ribbon diagrams of glutathione S-transferase allergens of *Tenebrio molitor*, *Locusta migratoria, Galleria mellonella, Musca domestica* and *Apis mellifera*. (D) Superimposition of the three-dimensional ribbon diagrams of glutathione S-transferase allergens of *Tenebrio molitor*, *Locusta migratoria, Galleria mellonella, Musca domestica* and *Apis mellifera*. (D) Superimposition of the three-dimensional ribbon diagrams of trypsin allergens of *Bombyx mori*, *Galleria mellonella, Hermetia illucens, Locusta migratoria* and *Musca domestica*. (E) Superimposition of the three-dimensional ribbon diagrams of hexamerin allergens of *Bombyx mori*, *Locusta migratoria*, *Galleria mellonella*, *Tenebrio molitor* and *Schistocerca americana*.

among insects and crustaceans, and it has been identified as an allergen of the fly maggot [28]. The hemolymph protein hemocyanin has been identified as an allergen of the German cockroach (Bla g 3) and American cockroach (Per a 3) and of the giant freshwater prawn *M. rosenbergii* as well (Allergome.org).

Owing to the conserved character, all the IgE-binding cross-reacting allergens of edible insects share very similar and readily superposable three-dimensional conformations. These structural similarities are illustrated in **Figure 2**, which shows the nice superposition of α -amylase, arginine kinase, glutathione S-transferase, trypsin, and hexamerin models of different origins. In fact, as shown for most of the members in different groups of evolutionary-related proteins, the three-dimensional conformations are much more conserved than the corresponding amino acid sequences.

4. Resistance of the insect allergens to proteolysis by digestive enzymes

Resistance to proteolysis consists of a property of paramount importance for food allergens, allowing them to escape the proteolytic degradation along the digestive tract and, thus, preserving their ability to stimulate the peripheral lymph nodes, e.g., Peyer's patches, associated with the intestinal tract. In this respect, all of the putative insect allergenic enzymes such as α -amylase, arginine kinase, glutathione S-transferase, and trypsin exhibit a number of predicted cleavage sites by pepsin and trypsin distributed along their polypeptide chain and, especially, exposed on their molecular surface (Figure 3). Accordingly, the multiple proteolysis of all of these enzymes by pepsin, trypsin, and chymotrypsin generate a number of amino acids and short peptides apparently devoid of efficient IgE-binding properties (Figure 3). However, a limited number of peptides would keep a sufficient size (>10 amino acid residues), to properly stimulate the digestive immune system. In this respect, the allergenicity of tropomyosin, myosin, α -amylase, and hexamerin from the yellow mealworm (*T. molitor*), the giant mealworm beetle (Zophobas atratus), and the litter beetle (Alphitobius diaperinus) was reduced but not abolished following both in vitro simulated gastric fluid (SGF) and in vitro simulated intestinal fluid (SIF) digestion and heat treatment [17, 29]. The heat resistance of the major allergens of edible insects implies that both cooked insects and insect protein-containing food products retain some intact allergenicity. Heat and proteolysis stability of tropomyosin from the mud crab (Scylla serrata) [30] and the tropical oyster Crassostrea belcheri [18] have been similarly pointed out.

5. What extent for the allergy to edible insects?

To date, only a few cases of allergenic manifestations caused by the consumption of edible insects have been reported in the literature. The first case reports deal with occupational allergies of particularly exposed environmental searchers, fishers, and food industry workers [21, 28, 31–37]. Similarly, the well-known "pancake syndrome" (oral mite anaphylaxis), caused by the unintended consumption of mite-contaminated foods, has been identified in Refs. [38, 39]. Interestingly, most or less severe cases of anaphylaxis caused by the ingestion

of various edible insects, reported in Chinese journals [40–51], were collated by Ji et al. [52], who counted up to 358 episodes of anaphylactic shock caused by food ingestion from 1980 to 2007. The most common offending allergens were identified as pineapple (25%), the soft-shelled turtle (Trionychidae) (19%), crabs (9%), and edible insects (locust + grasshopper)

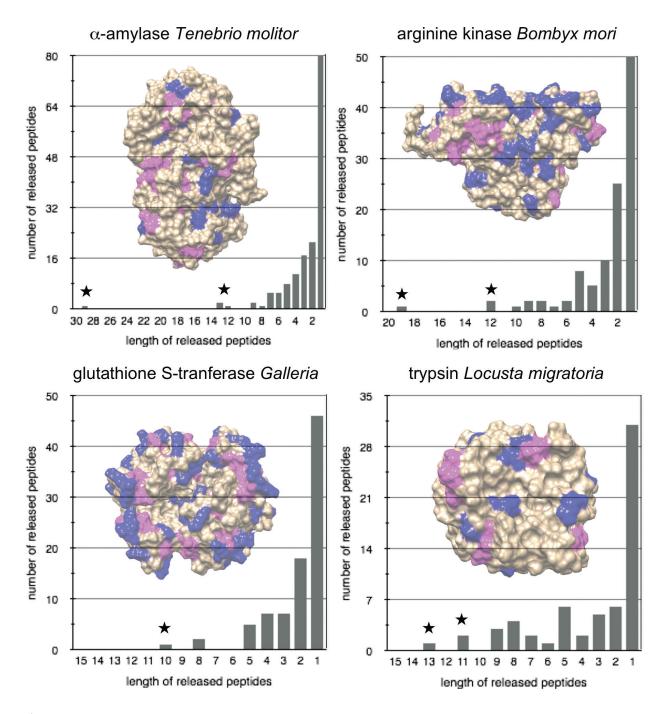


Figure 3. Size (number of amino acid residues) diagram of the peptides resulting from the predicted multiple proteolysis by pepsin, trypsin, and chymotrypsin of α -amylase of *Tenebrio molitor*, arginine kinase of *Bombyx mori*, glutathione S-transferase of *Galleria mellonella*, and trypsin from *Locusta migratoria*. Peptides of \geq 10 amino acid residues in length are indicated by stars (\bigstar). Overlay images showing the localization of the predicted cleavage sites by pepsin (pale grey) and trypsin (deep grey) on the molecular surface of the corresponding allergens are presented.

(14%). Other cases of anaphylaxis caused by the ingestion of edible insects were subsequently reported, mainly in Asia [53–55]. More recently, a majority of shrimp-allergic people (13 over 15) were confirmed as being allergic to yellow mealworm (*T. molitor*) when tested in double-blind, placebo-controlled food challenge (DBPCFC) [56]. In this respect, yellow mealworm appears as a food at least as allergenic as shrimps to trigger anaphylactic responses in shrimp-allergic patients.

The limited number of reported cases of anaphylaxis due to edible insect consumption seems to be largely underestimated, especially in countries like China, where a great variety of insects are traditionally consumed as a source of dietary proteins. The occurrence in all of the edible insects of IgE-binding allergens which cross-react with the major allergens tropomyosin and arginine kinase of shrimps, dust mites, mollusks, and even nematodes suggests that shrimp-allergic and mollusk-allergic patients are at risk when consuming edible insects or insect-containing food products. However, further large-scale investigations among a broad population of shrimp- and mollusk-allergic patients will be necessary to appreciate the real allergenic risk edible insects pose to previously sensitized individuals. In the meantime, it would be wise to inform the consumers for such a potential risk, e.g., by a proper labeling of insect foods and insect-containing food products.

6. Conclusion

Obviously, the repertoire of food allergens from edible insects consists of a number of IgE-binding cross-reactive allergens common to other arthropods, e.g., dust mites and crustaceans, mollusks, and, more scarcely, nematodes. These pan-allergens refer to muscle proteins, enzymes, and proteins with structural and physiological functions. However, the search of identities the insect proteins share with known allergens of the allergen bank as a criterion for identifying allergens of edible insects suffers from some limitations associated to the completeness and quality of the bank. Most of the allergenic proteins of animal or plant origin essentially belong to abundant and widespread protein families in both animal and plant species like tropomyosins, lipocalins, and caseins for animals and cupins, profilins, and prolamins for plants [57]. Moreover, depending on the data bank used for searching the identities with known allergens, the accuracy and exhaustiveness of the results might vary considerably. In this respect, the continuously updated FARRP AllergenOnline bank offers a maximum of guarantee for the retrieved information [58]. Accordingly, all of the allergens identified to date correspond to proteins already known for their allergenic properties. Other allergens more specific of insects remain to be identified and characterized, in order to have a more accurate idea about the variability and specificity of the edible insect allergens. A serological approach using IgE-containing sera from allergic patients will be necessary to fulfill such a requirement, instead of the computational approach reported in this chapter. As insect food could be so allergenic that it can trigger strong anaphylactic responses in allergic persons, it is recommended that all insect food and insect-containing food products should mention this allergy possibility very clearly in the product labels.

Author details

Pierre Rougé* and Annick Barre

*Address all correspondence to: pierre.rouge@free.fr

University Paul Sabatier – Tolouse 3, Research Institute for Development, Research Unit 152 Pharma-Dev, Faculty of Pharmacy, Toulouse, France

References

- [1] Rumpold BA, Schluter OK. Potential and challenges of insects as an innovative source for food and feed production. Innovative Food Science & Emerging Technologies. 2013;17:1-11.
- [2] DeFoliart G, Nakagaki B, Sunde M. Protein quality of the house cricket *Acheta domestica* when fed to broiler chicks. Poultry Science. 1987;**66**:1367-1371.
- [3] Belluco S, Losasso C, Maggioletti M, Alonzi CC, Paoletti MG, Ricci A. Edible insects in a food safety and nutritional perspective: a critical review. Comprehensive Reviews in Food Science and Food Safety. 2013;12:296-313.
- [4] Rumpold BA, Schluter OK. Nutritional composition and safety aspects of edible insects. Molecular Nutrition & Food Research. 2013;57:802-823.
- [5] Li L, Zhao Z, Liu H. Feasibility of feeding yellow mealworm (*Tenebrio molitor* L.) in bioregenerative life support systems as a source of animal protein for humans. Acta Astronautica. 2013;92:103-109.
- [6] van Huis A, Van Itterbeeck J, Klunder H, Mertens E, Halloran A, Muir G, Vantomme P. Edible Insects: Future Prospects for Food and Feed Security. FAO Forestry Paper 171, ISBN 978-92-5-107595-1. Rome: Food and Agriculture Organization of the United Nations; 2013.
- [7] Charlton AJ, Dickinson M, Wakefield, ME, Fitches E, Kenis M, Han R, Zhu F, Kone N, Grant M, Devic E, Bruggeman G, Prior R, Smith R. Exploring the chemical safety of fly larvae as a source of protein for animal feed. Journal of Insects as Food and Feed. 2015;1: 7-16.
- [8] Van der Brempt X, Moneret-Vautrin DA. The allergic risk of *Tenebrio molitor* for human consumption (article in French). Revue Française d'Allergologie. 2014;**54**:34-36.
- [9] Barre A, Caze-Subra S, Gironde C, Bienvenu F, Bienvenu J, Rougé P. Entomophagy and the risk of allergy (article in French). Revue Française d'Allergologie. 2014;**54**:315-321.
- [10] Van der Brempt X, Beaudoin E, Lavaud F. Is eating insects risky for allergic patients? (article in French). Revue Française d'Allergologie. 2016;**56**:186-188.

- [11] Barre A, Velazquer E, Delplanque A, Caze-Subra S, Bienvenu F, Bienvenu J, Benoist H, Rougé P. Cross-reacting allergens of edible insects (article in French). Revue Française d'Allergologie. 2016;56:522-532.
- [12] Daul CB. Slattery M, Reese G, Lehrer SB. Identification of the major brown shrimp (*Penaeus aztecus*) allergen as the muscle protein tropomyosin. International Archives of Allergy and Immunology. 1994;105: 49-55.
- [13] Santos ABR, Chapman MD, Aalberse RC, Vailes LD, Ferriani VPL, Oliver C, Rizzo MC, Naspitz CK, Arruda LK. Cockroach allergens and asthma in Brazil: Identification of tropomyosin as a major allergen with potential cross-reactivity with mite and shrimp allergens. The Journal of Allergy and Clinical Immunology. 1999;104:329-337.
- [14] Reese G, Ayuso R, Lehrer SB. Tropomyosin: An invertebrate pan-allergen. International Archives of Allergy and Immunology. 1999;119:247-258.
- [15] Galindo PA, Lombardero M, Borja JEG, Feo F, Barber D, García R. A new arthropod panallergen? Allergy. 2001;56:195-197.
- [16] Shafique RH, Inam M, Ismail M, Chaudhary FR. Group 10 allergens (tropomyosins) from house-dust mites may cause covariation of sensitization to allergens from other invertebrates. Annergy Rhinology. 2010:3:e74-e90.
- [17] Broekman H, Knulst A, den Hartog Jager S, Monteleone F, Gaspari M, de Jong G, Houben G, Verhoeckx K. Effect of thermal processing on mealworm allergenicity. Molecular Nutrition & Food Research. 2015;59:1855-1864.
- [18] Yadzir ZH, Misnan R, Bakhtiar F, Abdullah N, Murad S. Tropomyosin, the major tropical oyster *Crassostrea belcheri* allergen and effect of cooking on its allergenicity. Allergy, Asthma and Clinical Immunology. 2015;11:30.
- [19] Liu Z, Xia L, Wu Y, Xia Q, Chen J, Roux KH. Identification and characterization of an arginine kinase as the major allergen from silkworm (*Bombyx mori*) larvae. International Archives of Allergy and Immunology. 2009;**150**:8-14.
- [20] Verhoeckx KCM, van Broekhoven S, den Hartog-Jager CF, Gaspari M, de Jong GAH, Wichers HJ, van Hoffen E, Houben GF, Knulst AC. House dust mite (Der p 10) and crustacean allergic patients may react to food containing yellow mealworm proteins. Food and Chemical Toxicology. 2014;65:364-373.
- [21] Debaugnies F, Francis F, Delporte C, Doyen V, Lendent C, Mairesse M, Van Antwerpen P, Corraza F. Identification de l'α-amylase comme allergène du ver de farine chez des patients professionnellement exposés (article in French). Revue Française d'Allergologie. 2016;56:281.
- [22] Binder M, Mahler V, Hayek B, Sperr WR, Schöller M, Prozell S, Wiedermann G, Valent P, Valenta R, Duchêne M. Molecular and immunological characterization of arginine kinase from the Indian meal moth, *Plodia interpunctella*, a novel cross-reactive invertebrate pan-allergen. Journal of Immunology. 2001;167:5470-5477.

- [23] Srinroch C, Srisomsap C, Chokchaichamnankit D, Punyarit P, Phiriyangkul P. Identification of novel allergen in edible insect, *Gryllus bimaculatus* and its cross-reactivity with *Macrobrachium* spp. allergens. Food Chemistry. 2015;184:160-166.
- [24] Sahabudin S, Misnan R, Yadzir ZH, Mohamad J, Abdullah N, Bakhtiar F, Murad S. Identification of major and minor allergens of black tiger prawn (*Penaeus monodon*) and king prawn (*Penaeus latisulcatus*). The Malaysian Journal of Medical Sciences. 2011;18:2732.
- [25] Yadzir ZHM, Misnan R, Abdullah N, Bakhtiar F, Arip M, Murad S. Identification of the major allergen of *Macrobrachium rosenbergii* (giant freshwater prawn). Asian Pacific Journal of Tropical Biomedicine. 2012;2:50-54.
- [26] Rosmilah M, Shahnaz M, Zailatul HMY, Noormalin A, Normilah I. Identification of tropomyosin and arginine kinase as major allergens of *Portunus pelagicus* (blue swimming crab). Tropical Biomedicine. 2012;29:467-478.
- [27] Misnan R, Murad S, Yadzir ZH, Abdullah N. Identification of the major allergens of *Charybdis feriatus* (red crab) and its cross-reactivity with *Portunus pelagicus* (blue crab). Asian Pacific Journal of Allergy and Immunology. 2012;30:285-293.
- [28] Just N, Lièvre K, Lallemand K, Leduc V. Implication de l'hexamérine dans un cas d'allergie aux larves de mouches (article in French). Revue Française d'Allergologie. 2012;52:258.
- [29] Van Broekhoven S, Bastiaan-Net S, de Jong NW, Wichers HJ. Influence of processing and *in vitro* digestion on the allergic cross-reactivity of three mealworm species. Food Chemistry. 2016;196:1075-1083.
- [30] Huang YY, Liu GM, Cai QF, Weng WY, Maleki SJ, Su WJ, Cao MJ. Stability of major allergen tropomyosin and other food proteins of mud crab (*Scylla serrata*) by *in vitro* gastrointestinal digestion. Food and Chemical Toxicology. 2010;48:1196-1201.
- [31] Bernton HS, Brown H. Insects as potential sources of ingestant allergens. Annals of Allergy. 1967;25:381-387.
- [32] Meier-Davis S, Bush RK. Occupational sensitivity to *Tenebrio molitor* Linnaeus (yellow mealworm). The Journal of Allergy and Clinical Immunology. 1990;86:182-188.
- [33] Phillips J, Burkholder W. Allergies related to food insect production and consumption. The Food Insects Newsletter. 1995;8:1-2.
- [34] Teranishi H, Kawai K, Murakami G, Miyao M, Kasuya M. Occupational allergy to adult chironomid midges among environmental researchers. International Archives of Allergy and Immunology. 1995;106:271-277.
- [35] Freye HB, Esch RE, Litwin CM, Sorkin L. Anaphylaxis to the ingestion and inhalation of *Tenebrio molitor* (mealworm) and *Zophobas morio* (superworm). Allergy and Asthma Proceedings. 1996;17:215-219.

- [36] Aldunate MT, Echechipía S, Gómez B, García BE, Olaguibel JM, Rodríguez A, Moneo I, Tabat AI. Chironomids and other causes of fish food allergy. Alergología e inmunología clínica. 1999;14:140-145.
- [37] Meseguer Arce J, Sánchez-Guerrero Villajos IM, Iraola V, Carnés J, Fernández Caldas E. Occupational allergy to aquarium fish food: Red midge larva, freshwater shrimp, and earthworm. A clinical and immunological study. Journal of Investigational Allergology and Clinical Immunology. 2013;**23**:462-470.
- [38] Sánchez-Borges M, Capriles-Hulett A, Fernández-Caldas E, Suárez-Chacón R, Caballero F, Castillo S, Sotillo E. Mite-contaminated foods as a cause of anaphylaxis. The Journal of Allergy and Clinical Immunology. 1997;99:738-743.
- [39] Sánchez-Borges M, Suárez-Chacón R, Capriles-Hulett A, Caballero-Fonseca F, Iraola V, Fernández-Caldas E. Anaphylaxis from ingestion of mites: Pancake anaphylaxis. The Journal of Allergy and Clinical Immunology. 2013;131:31-35.
- [40] Wei SZ, Jia LL, Wang SX. A case of anaphylactic shock caused by silkworm pupa (article in Chinese). Chinese Journal of Medicine. 1981;299:43.
- [41] Cheng XL, Lin HZ, Zhang SY. Successful curative treatment of a patient with anaphylactic shock caused by ingestion of silk worm pupa (article in Chinese). Guangzhou Med. 1987;3:36.
- [42] Wang YL, Niu CX, Liu Y. Three cases of anaphylactic shock caused by ingestion of silkworm pupa (article in Chinese). China Journal of Leprosy and Skin Diseases. 1999;15:56-57.
- [43] Qiao X. A case of anaphylactic shock caused by locust consumption (article in Chinese). Medical Journal of the Chinese People's Armed Police Forces. 1999;7:414.
- [44] Zhang H. A case of anaphylactic shock caused by ingestion of silkworm pupa (article in Chinese). Lit. Inf. Prev. Med. 2002;8:458-459.
- [45] Pao DH, Zhao, GS. A case of anaphylactic shock caused by cicada pupa consumption (article in Chinese). People's Military Surgeon. 2003;**46**;246.
- [46] Wan YF, Wei ZF. A case of anaphylactic shock caused by bee pupa consumption (article in Chinese). Clinical Journal of Medical Officer. 2003;**31**:52.
- [47] Wang Y, Feng SH. A case of anaphylactic shock caused by ingestion of bee larva (article in Chinese). Medical Journal of National Defending Forces in Southern China. 2003;13:346.
- [48] Wang DJ, Zhang DL, Yang FX, Chen YZ, Wei L, Yang HX et al. Eight cases of severe type-1 allergic reaction caused by consumption of silkworm pupa (article in Chinese). Henan Journal of Preventive Medicine. 2005;16:148.
- [49] Liu XP. Nineteen cases of anaphylactic shock caused by grasshopper consumption (article in Chinese). China Modern Doctor. 2007;**45**:41.

- [50] Zhang YZ. A case of anaphylactic reaction caused by ingestion of *Clanis bilineata* (article in Chinese). Clinical Wrong Diagnosis and Wrong Therapy. 2007;**20**:125.
- [51] Ji KM, Zhan ZK, Chen JJ, Liu ZG. Anaphylactic shock caused by silkworm pupa consumption in China (article in Chinese). Allergy. 2008;63:1407-1408.
- [52] Ji K, Chen J, Li M, Liu Z, Wang C, Zhan Z, Wu X, Xia Q. Anaphylactic shock and lethal anaphylaxis caused by food consumption in China. Trends in Food Science and Technology. 2009;20:227-231.
- [53] Choi GS, Shin Y, Kim JE, Ye YM, Park HS. Five cases of food allergy to vegetable worm (*Cordyceps sinensis*) showing cross-reactivity with silkworm pupae. Allergy. 2010;**65**:1196-1197.
- [54] Yew KL, Kok VSL. Exotic food anaphylaxis and the broken heart: sago worm and Takotsubo cardiomyopathy. The Medical Journal of Malaysia. 2012;5:540-541.
- [55] Okezie OA, Kgomotso KK, Letswiti MM. Mopane worm allergy in a 36-year-old woman: a case report. Journal of Medical Case Reports. 2010;4:42.
- [56] Broekman H, Verhoeckx KC, den Hartog Jager CF, Kruizinga AG, Pronk-Kleinjan M, Remington BC, Bruijnzeel-Koomen CA, Houben GF, Knulst AC. Majority of shrimp-allergic patients are allergic to mealworm. The Journal of Allergy and Clinical Immunology. 2016;137:1261-1263.
- [57] Radauer C, Bublin M, Wagner S, Mari A, Breiteneder H. Allergens are distributed into few protein families and possess a restricted number of biochemical functions. The Journal of Allergy and Clinical Immunology. 2008;121:847-852.
- [58] Sircar G, Sarkar D, Bhattacharya SG, Saha S. Allergen databases. Methods in Molecular Biology. 2014;1184:165-181.

