



Review

Current advances in ant venom proteins causing hypersensitivity reactions in the Asia-Pacific region

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ABSTRACT

The main insects causing allergy reactions to stinging insect in humans are Apidae (bees), Vespidae (wasps, yellow jackets and hornets) and Formicidae (ants). Their venom stings are composed of various biologically active peptides and protein components, some of which can cause toxicity or anaphylaxis in humans. The protein venom demonstrate some common allergenic activity such as for fire ants and vespids, which have two common allergens that are phospholipase A₁ (enzymatic activity) and antigen 5 with unknown biological activity. The common allergens seem to share some degree of immunological cross-reactivity, particularly when the sequence homology is above 70%. Therefore immunotherapeutic approaches targeting more than one specific species are of interest. Recent widespread increases of various ant species in many countries have resulted in higher number of reported about serious allergic reactions to stings. Most insect-allergy related cases have been reported for species from *Solenopsis*, *Myrmecia* and *Pachycondyla* genera, and their stings can often result in human fatalities. In addition, stinging ants can have serious health effects on livestock, agricultural damage adversely affecting the biodiversity of the region. This review discusses the impact of important ant species on human health in the Asia-Pacific region along with the molecular immunological aspects of the identified venoms and current status of diagnostics and therapeutics.

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1. Introduction

Insect venom of the order Hymenoptera such as bees, hornets, wasps, yellow jacket and ants are responsible for causing severe insect sting allergic reactions in approximately 1% of children and 3% of adults (Golden, 2003). The phylogenetic relationships of the Hymenoptera are outlined in Fig 1. Every year large numbers of people are stung by these insects, and this is an increasing serious problem in tropical regions. The venom of these insects

are composed of various biologically active peptides and protein components, some of which can cause toxicity or anaphylaxis in humans (Barnard, 1973). The venom allergens of fire ants, jack jumper ants (JJAs), bees and vespids are sequences and listed in Table 1. Almost all known venom allergens are proteins between 10 and 50 kDa in size and composed of 100–400 amino acid residues. The one exception is the JJA venom allergenic peptide, which is 2–8 kDa in size and consisted of 25–50 amino acid residues.

Ants are globally found with roughly 8800 species exist in the family Formicidae, but a few causing allergic reactions (Fig 1). Their colonies are normally situated near a place of residence and can have a negative effects on agricultural products. Ecologically, fire ants may reduce biodiversity, impacting on other ant species, invertebrates, reptiles and even birds and mammals (deShazo et al., 1990). The risk of ant sting anaphylaxis depends on complex interactions between the aggression, local distribution, venom allergenicity and likelihood of human contact. The sting causes a fiery sensation and can be a serious harm if a victim is immediately stung by a great number of ants and contains

Abbreviations: JJA, jack jumper ant; Sol i, *Solenopsis invicta*; Sol r, *Solenopsis richteri*; Sol s, *Solenopsis saevissima*; WBE, whole body extract; VIT, venom immunotherapy.

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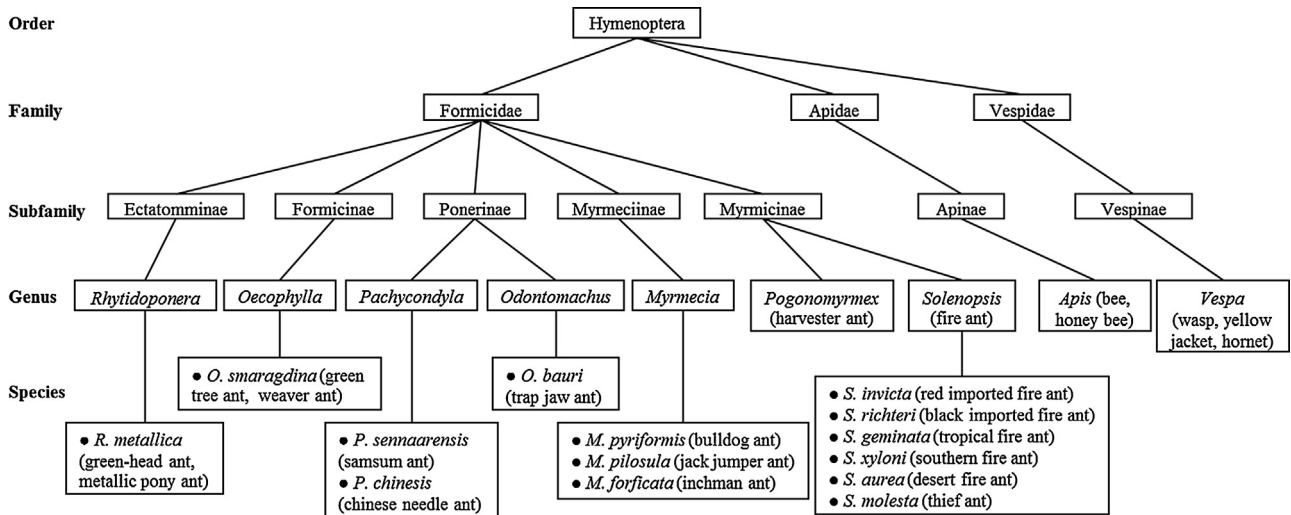


Fig. 1. Taxonomy of Hymenoptera, including ants that cause allergic reactions in the Asia-Pacific region.

Table 1
Allergenic protein groups of Hymenoptera venom in Asia-Pacific.

Allergen	IgE prevalence	Molecular weight ¹ (kDa)	Amino acids residues ²	Activity and Common name	Reference
Imported fire ant (<i>Solenopsis invicta</i>)					
Sol i 1	87%	37	309	Phospholipase A ₁	(Hoffman et al., 2005; Hoffman et al., 1990)
Sol i 2	61%	26/dimer	238/dimer	Unknown	(Hoffman et al., 1990; Schmidt et al., 1996)
Sol i 3	61%	24	212	Antigen 5	(Hoffman et al., 1990; Schmidt et al., 1993)
Sol i 4	74%	13.3	117	Unknown	(Hoffman et al., 1990)
Chinese needle ant (<i>Pachycondyla chinensis</i>)					
Pac c 3	23%	23	206	Antigen 5	(Lee et al., 2009)
Jack jumper ants (<i>Myrmecia pilosula</i>)					
Myr p1	52%	5–8	45	Haemolytic activity Inhibits B cell proliferation	(Davies et al., 2004; Donovan et al., 1993)
Myr p2	35%	2–4	26–27	Unknown	(Davies et al., 2004; Street et al., 1996)
Myr p3	–	4	36	Antimicrobial activity and low hemolytic activities	(Inagaki et al., 2004)
Honey bee (<i>Apis mellifera</i>)					
Api m 1	10–80%	16	134	Phospholipase A ₂	(Dudler et al., 1992)
Api m 2	70–100%	45	349	Hyaluronidase	(Gmachl and Kreil, 1993)
Api m 3	37%	49	373	Acid phosphatase	(Soldatova et al., 2000)
Api m 4	0–10%	3	26	Melittin	(King et al., 1976)
Api m 5	42%	100	752	Dipeptidyl-peptidase	(Blank et al., 2010)
Api m 6	50%	8	71	Serine protease inhibitor	(Michel et al., 2012)
Api m 7	–	45	393	CUB serine protease	(Georgieva et al., 2010)
Api m 8	46%	70	536	Carboxylesterase	(Blank et al., 2010)
Api m 9	–	60	449	Serine carboxypeptidase	(Blank et al., 2010)
Api m 10	>60%	50–55	223	Icarapin	(Blank et al., 2011)
Paper wasp (<i>Polistes annularis</i>)					
Pol a 1	–	34	301	Phospholipase A ₁	(Pantera et al., 2003)
Pol a 2	–	38	338	Hyaluronidase	(Pantera et al., 2003)
Pol a 5	–	23	205	Antigen 5	(Lu et al., 1993; Pantera et al., 2003)
Yellow jacket (<i>Vespa vulgaris</i>)					
Ves v 1	58–100%	34	300	Phospholipase A ₁	(King et al., 1996)
Ves v 2	76%	38	331	Hyaluronidase	(King et al., 1996)
Ves v 3	50%	100	751	Dipeptidyl-peptidase	(Blank et al., 2010)
Ves v 5	17–100%	23	204	Antigen 5	(Lu et al., 1993)
European hornet (<i>Vespa crabro</i>)					
Vesp c 1	–	34	301	Phospholipase A ₁	(Hoffman et al., 2005)
Vesp c 5	–	23	202	Antigen 5	(Lu et al., 1993)
White-Faced Hornet (<i>Dolichovespula maculata</i>)					
Dol m 1	–	34	303	Phospholipase A ₁	(Soldatova et al., 1993)
Dol m 2	–	38	331	Hyaluronidase	(Lu and Kochoomian, 1995)
Dol m 5	–	23	204	Antigen 5	(Fang et al., 1988)

¹ Several allergens are glycoproteins, and the molecular weight refers to only the protein portion.

² Almost allergens contain signal sequence and propeptides, and the amino acid showed only mature peptides.

about 10–100 ng protein per sting (Hoffman et al., 1988a). The different ant venom shares some common protein components, but each group shows also a number of unique allergen components. Although the direct ant sting venom does usually not cause fatal allergic reactions, anaphylactic reactions may be more common in regions where these ants are common and humans are frequently stung (Rhoades, 2001).

The medical treatment data for allergenic ant sting has been foremost developed for imported fire ant. Immunotherapeutics have been developed using whole body extract (WBE) rather than pure venom. The report about the strong efficiency of purified ant venom immunotherapy (VIT) has been shown in the double blind randomized placebo-controlled with the JJA in Australia (Brown et al., 2003b). However, there are still very limited data available for other ant groups. The main objective of this review is to provide a brief summary of the present history, geographical distribution and recent developments in studies relating to ant venom allergy and immunotherapy in the Asia-Pacific region.

2. Invasion history

Invasive fire ant species pose great threats to agriculture, natural environments, and public health. Some species can displace native fauna, reduce biodiversity, serve as pathogen vectors, or impair ecosystem services. Fire ants of the genus *Solenopsis* have rapidly spread over parts of the tropical world from their native habitats in South America (Hoffman, 1995). More recently, fire ants have been introduced to California, and other regions of the world, including the southern United States, Pacific Islands (Lai et al., 2009), Southeast Asia (Knight and Bangs, 2007; Wu et al., 2008), and Middle East (Khan et al., 1999). In the southeast United States, the stings of imported fire ants are the most common cause of insect venom anaphylaxis (Partridge et al., 2008).

The first case of anaphylaxis from red imported fire ant, *Solenopsis invicta* (*S. invicta*) stings reported in Spain documented that these ants were obscured in transported wood shipping from South America (Fernandez-Melendez et al., 2007). Recently, it was found that these ants entered many countries via shipping containers as shown in Fig 2 which now can be found in Southern China (Wu et al., 2008), Singapore (Thong et al., 2005) and Southeast Asia (Knight and Bangs, 2007), as well as north Australia (Solley et al., 2002). The tropical red fire ant, *Solenopsis geminata* (*S. geminata*), a native of the southern United States, Central to northern South America, is a well-known tramp species and has become a serious problem in Taiwan since the 1980th (Lai et al., 2009) as well as in Indonesia (Knight and Bangs, 2007), Thailand (Sukprasert et al., 2012) and can spread across many Asia-Pacific islands. This ant is a non-native species to Australia, which was first reported in Darwin. There have been reports of 10 cases of anaphylactic reactions to the black imported fire ant, *Solenopsis richteri* (*S. richteri*) sting that were admitted to Najran General Hospital. Furthermore, the *Pachycondyla sennaarensis* (samsum ant) have been present in Saudi Arabia (Al-Shahwan et al., 2006; Khan et al., 1999). The Chinese needle ant, *P. chinensis* was a species introduced into North America over 70 years ago and now is found in Georgia, South Carolina, North Carolina, Virginia and throughout Southeast Asia (Nelder et al., 2006). The ants of the *Myrmecia* species are JJAs and bulldog ants, both are primitive species in Australia and Tasmania (Shek et al., 2004). The JJA is especially found in rural Victoria, southern New South Wales and cooler areas of South Australia and Western Australia (Weber, 2010) as shown in Fig 2.

2.1. *Myrmecia* species

At least 89 *Myrmecia* species were identified, however only two are well-known namely, the JJA (*M. pilosula*), which is small

around 10 mm in length, a carnivore and scavenger and, the bull ant (*M. pyriformis*), a larger ant of about 15–20 mm, with a powerful sting, fast movements and aggressive nature. Usually anaphylactic reactions in Australia are caused by *M. pilosula* and *M. pyriformis* species. Fatalities are rare and reports showed mean national annual incidence of 0.02 deaths per million populations per year in the period 1980–1999 (McGain and Winkel, 2002). Although allergy is common in southeastern Australia, only 4 deaths have been reported from the southern island of Tasmania (population 223,000) between 1980 and 1999 (Brown et al., 2001). The systemic reactions caused by stings from ants in the genus *Myrmecia* are important for IgE-mediated anaphylaxis in the rural or outskirts of southeastern Australia, with prevalence rates of about 2–3% of exposed populations (Douglas et al., 1998). There are reports that the rate of clinical systemic reactions to *M. pilosula* venom in Tasmania is 2.7% (95% CI, 1.8–3.9), as compared to 0.6% for wasp stings. Furthermore, the allergy prevalence seems to be related to age and exposure rate and there is a higher systemic reaction risk as compared to mainland Australia (Brown et al., 2003a).

The venoms of JJA and bulldog ants contain phospholipases, but the allergens present appear to be a complex series of extremely basic peptides (Table 1) (Davies et al., 2004; Inagaki et al., 2004). These peptides possess potent allergenic properties and in addition demonstrate strong antimicrobial and cytotoxic activities. Preliminary studies of serum from allergic patients to *Myrmecia* species venom determined no evidence of cross-reactivity to other venom allergens. Furthermore, a single species of bulldog ant, *M. gratioiosa*, presents the main cause for ant sting anaphylaxis in the Perth area. Systemic reactions ranged in severity from mild (one patient), moderate (seven patients) to severe with hypotension (four patients) (Gilhotra and Brown, 2006). In addition Solley (1989) reports 17 allergic sting reactions caused by *Rhytidoponera metallica*, green-head ants in Queensland Australia.

2.2. *Pachycondyla* species

These are winged ants that have a small habitat near woodlands, in rotten wood and in old wooden houses (Fukuzawa et al., 2002). Their venoms are an important cause of allergenic reactions, including anaphylaxis in Asia and Middle East (Shek et al., 2004). In Korea, *Pachycondyla chinensis* species has been reported a major cause of ant sting venom allergy (Cho et al., 2002), commonly called Chinese needle ant or Asian needle ant. Approximately 2.1% of adults living in an ant-infested area had immediate type allergic responses to ant stings. These patients had positive skin prick tests and increased levels of serum-specific IgE to *P. chinensis* extract as compared to the rest of residents in the same area. The author suggested that there might be a possible cross-reactivity between bee venom and *P. chinensis* venom. There are reports of *P. chinensis* causing allergic reaction in neighbouring Japan (Fukuzawa et al., 2002).

Studies with allergic patients against *P. chinensis* venom showed the presence of eight IgE-binding proteins (58, 46, 31, 29, 27, 25, 22, and 12 kDa) and one major allergen (12 kDa) recognised by 85% of patient sera tested (Kim et al., 2001). Some bee allergic patient sera showed cross-reactivity, however those with only *Pachycondyla* venom allergy did not cross-react to bee venom. ELISA inhibition tests showed evidence of cross-reactivity with yellow jacket. However, there were low cross-reactivity levels with wasp or imported fire ants and *P. chinensis*. Thus, allergic patients to *P. chinensis* are unlikely to have successful immunotherapy with imported fire ant extract. Future immunotherapy must develop to focus on species specific therapeutics. The stinging ant of *P. sennaarensis* species, commonly known as the samsum ant can cause allergic reactions and are found in the United Arab Emirates (UAE) (Dib et al., 1995). The *P. sennaarensis* species are also found in the Arabian Peninsula and African tropics and have stings that are very painful. The UAE

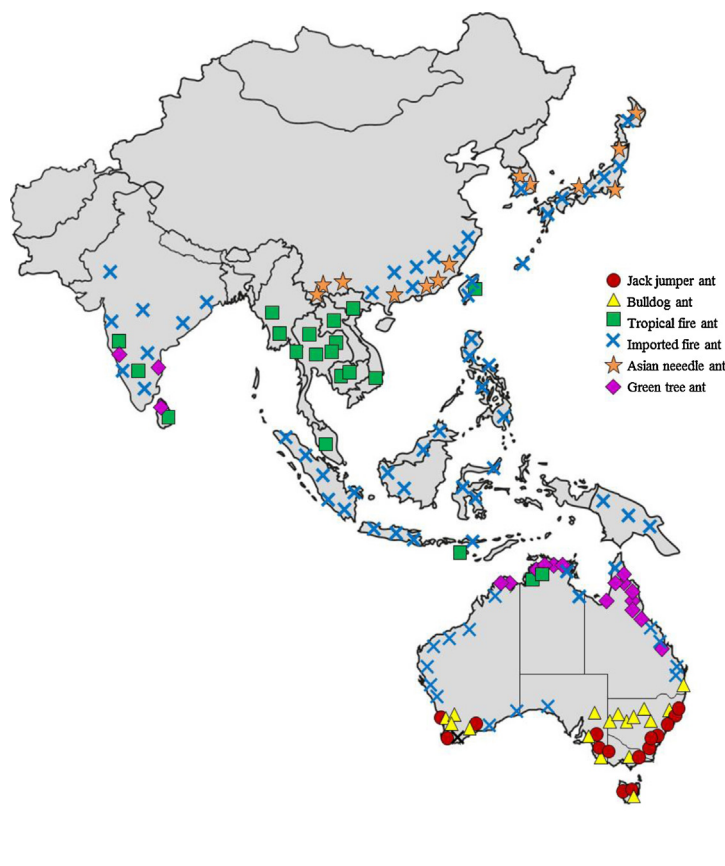


Fig. 2. Geographical distribution of ant sting causing allergic reactions to various ants in the Asia-Pacific region.

recorded that four deaths within 4 years were caused by anaphylactic shock after the sting. The results of skin tests and specific IgE to *P. senaarensis* were both 97% positive for patients with anaphylactic reactions. Furthermore, Reunala et al. (2005) reports 10 sera of allergy patients to *P. senaarensis* venom binding to the 24 kDa (Sol i 3) allergen of the *S. invicta* and three sera showed IgE binding to the 13 kDa (Sol i 2 and/or Sol i 4) allergen. However, clinical cross-reactivity does not seem to be important.

2.3. *Solenopsis* species

Fire ants (*Solenopsis* sp.) are members of the Formicidae family and include over 200 species worldwide. These ants disrupt mechanised farming and damage crops. The medically important aggressive species are *S. invicta*, *S. richteri*, *S. geminata* and *S. saevissima* (Hoffman, 1997; Tankersley, 2008). The majority of the fire ant venom consists of 90–95% basic piperidine alkaloids that are highly cytotoxic, neurotoxic and hemotoxic. Although this component has no allergenic properties, it is responsible for the characteristic pustules seen after a fire ant sting. The aqueous phase contains four major allergenic proteins (Hoffman et al., 1988a). A single fire ant sting contains only 1–10 ng of protein that can cause specific IgE antibody production (Hoffman, 1995). A recent study investigated the alkaloid components and found them to be much more complex than previously thought. Alkaloid compositions are present in many species of fire ants venom. The report about anaphylactic near fatal reactions to *S. geminata* sting venoms occurred with two members of the U.S. military stationed in Guam and Okinawa, Japan. It demonstrated the strong cross-reactivity to the native sting venoms, because these soldiers had allergic reactions to *S. invicta* stings before (Hoffman, 1997). Normally, ant allergy is a rare problem in India, however there is a recent report of a one and half year old

male child with good health and no previous allergy history to ant who suffered severe anaphylaxis reaction due to *S. geminata* (about 10–20 mm small ants as shown in Fig 3A) (Havaldar et al., 2012).

Four allergenic proteins have been isolated from *S. invicta* venom and characterized (Hoffman et al., 1988a). Sol i 1 has phospholipase A₁ property that is also found in vespid venoms and belongs to the lipoprotein lipase family (Hoffman et al., 1988b; Hoffman et al., 2005). A 3-dimensional model of Sol i 1 is shown in Fig 4A, and demonstrating the highly conserved active site and core region of the molecule. It contains carbohydrates determinant, but there is some evidence of the IgE reactivity against protein determinants and showed some cross-reactivity with yellow jacket, wasp and honeybee venom phospholipase, see Fig 5A (Hoffman, 2010). Sol i 2 make up two thirds of the venom protein and the crystal structure of recombinant protein was recently determined by Borer et al., (2012). It is composed of two identical monomers, which have 3 intra- and 1 inter-molecular disulfide bonds and contains carbohydrate determinants (Fig 4B). The protein is a member of a unique protein family (Schmidt et al., 1996; Schmidt et al., 1993). In Fig 5B, other similar venom proteins to Sol i 2 of the *Solenopsis* species are *S. geminata* (Sol g 2), *S. richteri* (Sol r 2) and *S. saevissima* (Sol s 2) (Hoffman, 1997). Sol i 2 generate the production of IgE antibody in about one-third of individuals stung by fire ants. Sol i 2 proteins are less stable than Sol i 3 proteins. In Fig 5C, Sol i 3 demonstrates its relationship to members of the antigen 5 protein family of vespid venom proteins (Schmidt et al., 2003), but does not show cross-reactivity with vespid venom antigen 5 (Padavattan et al., 2008). The crystal structure of Sol i 3 determined shows that the overall structure is very similar to Ves v 5 and there are some amino acid sequences that are relatively conserved. However, Sol i 3 showed four non-conserved IgE epitopes coloured in Fig 4C.

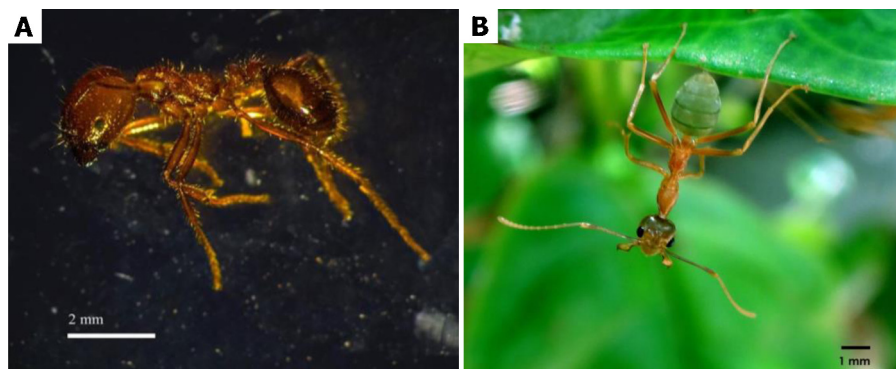


Fig. 3. Ecological overview of ants causing allergies. A: Tropical fire ant (*Solenopsis geminata*) workers are between 2 and 5 mm long and the queen is notably larger than the workers at about 8 mm and has an attractive red-orange colour. B: Green tree ant (*Oecophylla smaragdina*), usually 6–8 mm long with a bright green gaster and build their nest by weaving leaves together using larvae's silk. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

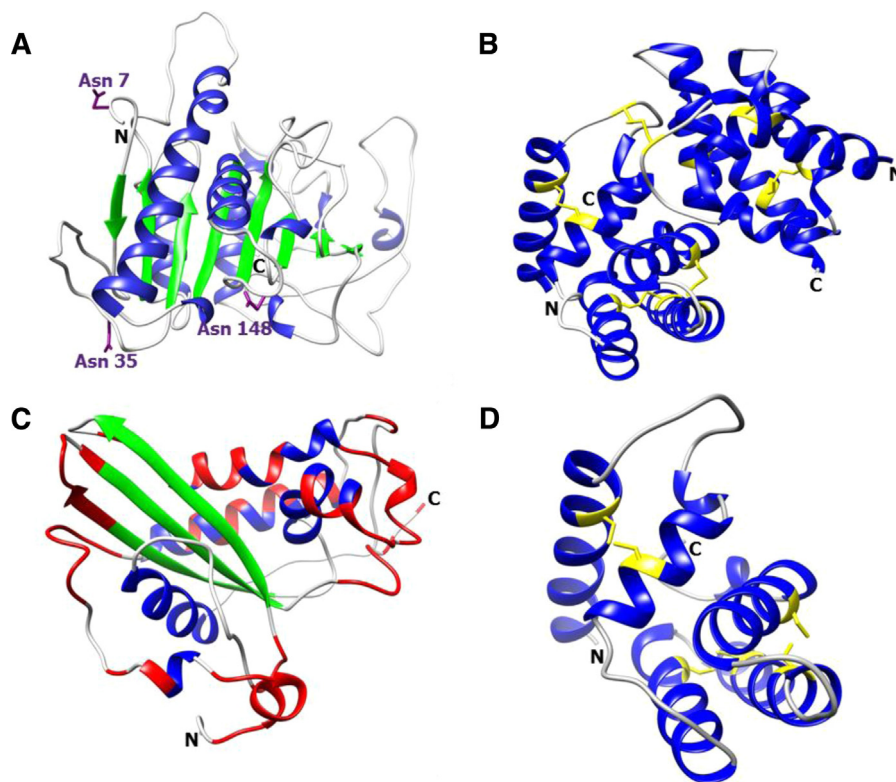


Fig. 4. Ribbon modeling structures of allergenic proteins from *S. invicta* venom. The overall structure shows in different colors which blue color is α -helix, gray color is random coil and green color is β -sheet. A: Sol i 1 (Genbank no. AAT95008) allergen show potential N-linked glycosylation positions (purple ligands), B: Sol i 2 allergen which published in PDB ID no. 2YGU is composed of two monomers which have three intra- and one inter-molecular disulfide linkages (yellow), C: Sol i 3 (Genbank no. AAB65434) allergen shows IgE antibody-binding with four non-conserved epitopes highlighted in red, D: Sol i 4 (Genbank no. AAC97369) allergen shows 36.75% amino acid identity with the Sol i 2 monomer structure and composed of three intramolecular disulfide bonds (yellow).

Although the protein compositions of fire ant venoms have been extensively investigated, Sol i 2 and 4 proteins have not been found in other venoms and are not similar to other known proteins (Hoffman et al., 1988a). These two proteins are related with each other, but Sol i 4 lacks the dimerizing cysteine residues and is present as a monomer form as compared to the intramolecular disulfide bonds in Sol i 4 as shown in Fig 4D. Sol i 4 is a unique protein family and relate to *S. geminata* (Sol g 4) venom as demonstrated in Fig 5D. In some endemic regions, 30–50% of the population shows evidence of sensitization via serum-specific IgE antibodies to *S. invicta* (Partridge et al., 2008). There are reports about incidence of anaphylactic reactions caused by *S. invicta* stings in the Asia-Pacific region. Especially in Brisbane, Australia, these

ants sting have caused anaphylactic reaction. If the red imported fire ant continuously spread in Australia, it is estimated that this fire ant will be responsible for up to 3000 anaphylaxis reactions each year by 2030 (Solley et al., 2002).

Other species of fire ants venom including *S. geminata*, *S. richteri*, *S. xyloni*, *S. aurea* are highly cross-reactive with *S. invicta* (Hoffman, 1997; Hoffman et al., 1990). While the *S. richteri* species seems only to contain Sol i 1 and 3 allergens (Hoffman, 2010), the Sol 2 antigens showed high immunological cross-reactivity among the species, but may exhibit species-specific epitopes. Mouse monoclonal antibodies that are species-specific have been produced, however they don't appear to be important for specificity of human IgE cross-reactivity (Hoffman, 1997; Hoffman et al., 1990).

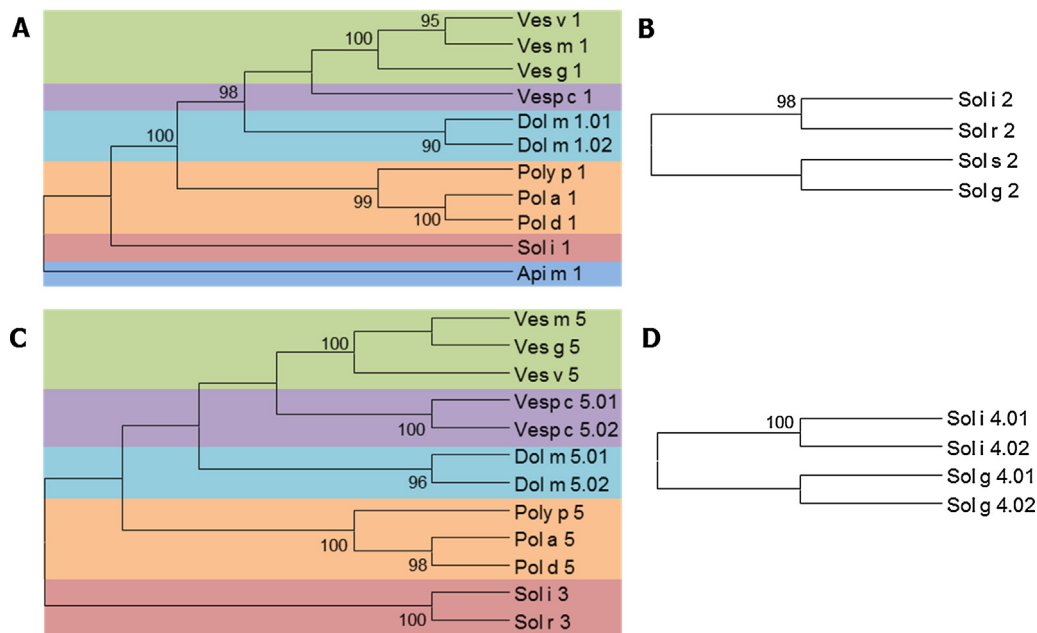


Fig. 5. Phylogenetic tree for amino acid sequences of 4 allergenic protein groups between the ant groups, *Solenopsis invicta* (Sol i), *Solenopsis richteri* (Sol r), *Solenopsis saevissima* (Sol s) and the vespid groups, *Apis mellifera* (Api m), *Polistes annularis* (Pol a), *Vespula vulgaris* (Ves v), *Vespa crabro* (Vesp c), *Dolichovespula maculata* (Dol m), *Vespula maculifrons* (Ves m), *Polistes dominula* (Pol d), *Vespula germanica* (Ves g), *Polybia paulista* (Poly p). A: phospholipase A₁ groups have been isolated from various vespid and ant species, B: allergenic protein group 2 from *Solenopsis* species, C: antigen 5 groups have been isolated from various vespid and ant species, D: allergenic protein group 4 from *Solenopsis* species.

2.4. Other species

Other species of ants and their venoms have been rarely reported to cause allergic reactions. In Venezuela, a child after being stung with *Odontomachus bauri* developed strong allergic reaction in 2002 (Rodriguez-Acosta and Reyes-Lugo, 2002). In Korea there were reports of patients with allergic reaction caused by ant stings to *Ectomomyrmex* species (Kim and Hong, 1992) and *Cataglyphis bicolor* species caused allergic reaction in Egypt (Sanad et al., 2002). There are reports to ant bites, which caused fatal anaphylaxis in Sri Lanka. One case was a patient stung by a queen of *Odontomachus simillimus*, found in the wet zone, and died after 18 h admission and another patient was stung by a worker of *Tetraponera rufonigra* (Ratnatilaka et al., 2011). In Northern Australia the *Oecophylla smaragdina* species, which are wildly named weaver ant, green tree ant and orange gaster ant, caused some anaphylactic reactions (Fig 3B). Whether other ant species are present in the Asia-Pacific region causing allergic reactions is not known and limited to scientific reports.

3. Clinical symptoms

The clinical symptoms after being stung by the various ant species in the Asia Pacific region ranged from painful, skin redness, urticaria, itching, small and large local reactions and in some cases fatal anaphylaxis. Reactions to the *S. invicta* stings may generate any types of allergic reactions, however almost all stung people report immediate wheal and flare reaction, a sterile pustule and a large local reaction at the site of sting followed by the development of characteristic pustule after 24 h and sometimes lasting several days, which intense pruritus (deShazo et al., 1990). A report of a 2-year-old male infant with multiple red imported fire ant stings developed both anaphylaxis and toxin-mediated systemic reactions, including rhabdomyolysis and renal failure (Cochran et al., 2013). Hence, there are five different reactions classified as: normal, large local, rare, toxic and systemic

(anaphylaxis). A normal reaction is confined to the site of the sting and appears as mild erythema, swelling and pain. A large local reaction is characterized by extensive erythema and immediate wheal and flare followed by the development of characteristic pustule after 24 h and sometimes lasting several days, which intense pruritus. Rare reactions are characterized by serum sickness which consists of angioedema, urticaria, malaise and fever about 7 days after the sting (Brown et al., 2004). The incidence of repeat sting with these individuals can cause anaphylaxis reaction and therefore requires immunotherapy when skin test results are positive. Other rare reactions include nephritic, vasculitic, neurological and encephalitic-like reactions and can appear up to 2 weeks after the sting. Toxic reactions take place after multiple contemporary stings that result in cardiovascular collapse, hypotension and possibly death. Serious systemic (anaphylaxis) reactions are mediated by specific IgE antibodies to venom allergens. This results through activation of mast cells followed by mediator release and systemic symptoms of anaphylaxis. Patients with history of anaphylaxis to previous stings can have anaphylaxis with repeat stings with about 60% of adult patients and 20–32% of children (Georgy and Saltoun, 2012; Koterba and Greenberger, 2012). Immunotherapy is indicated for anaphylactic reactions of patients who have a history of anaphylaxis and positive skin prick test results (venom specific IgE antibody).

The *M. pilosula* and *M. pyriformis* venoms may produce only mild skin irritation to the majority of humans but also severe anaphylactic response in sensitized victims (Hodgson, 1997). The sting of the fire ant, *Solenopsis* species causes an immediate burning sensation and development of characteristic sterile pustule after 18–24 h as a result of toxic alkaloids in the venom that derived from piperidines such as solenopsin A. These alkaloids are 2, 6-di-substituted piperidines which have antibacterial, histamine-releasing, haemolytic, insecticidal and cytotoxic properties (Jouvenaz et al., 1972; Lind, 1982; Yi et al., 2003). The alkaloids do not generate IgE antibody responses but the allergenic proteins in the venom, which comprise only 0.01% of the venom by weight,

Table 2

The incidence of diagnosis from ant stings allergy, mainly in the Asia-Pacific region.

Species	Incidence of diagnosis ^a	Severity of disease	Years	References
<i>Solenopsis</i>	2 US servicemen near fatalities in Japan	Life-threatening anaphylaxis	Unspecified	(Hoffman, 1997)
	A 47 year-old patient in Australia	Anaphylaxis reactions	1999–2000	(Solley et al., 2002)
	A 60 year-old patient in Indonesia	Severe cutaneous allergic vasculitis	2002	(Knight and Bangs, 2007)
	A one and half year-old child near fatality in India	Severe anaphylactic reactions with a clinical diagnosis	Unspecified	(Havaladar et al., 2012)
	A 3 year-old child death in India	Severe life-threatening anaphylaxis	2014	(Purkait et al., 2014)
<i>Myrmecia</i>	4 deaths and 2 patients in Australia	Moderate to systemic reactions	1980–1999	(McGain and Winkel, 2002)
	10 patients in Western Australia	Range from mild, moderate and severe with hypotension	2004	(Gilhotra and Brown, 2006)
	265 participants in Australia	Clinical reactivity	2006–2007	(Brown et al., 2011)
<i>Pachycondyla</i>	4 deaths and 31 patients in UAE	Anaphylactic shock and systemic reactions	1991–1995	(Dib et al., 1995)
	7 patients in Korea	Systemic reactions with allergenic disease	Unspecified	(Kim et al., 2001)
	10 patients in UAE	Severe type I allergic reactions	Unspecified	(Reunala et al., 2005)

^a The evidences are showed only in the area under this study.

can induce IgE production in allergic patients to fire ant stings (Hoffman et al., 1988a).

4. Diagnosis

The circumstances surrounding the ant sting incident should be ascertained, especially the activity of patients and the insect behaviours in the area while they were stung. Taking the insect for identification is recommended. The incidence of diagnosis from ant sting allergy in the Asia-Pacific region is outlined in Table 2. Cho et al. (2002) reports about 7 patients in Korea with anaphylaxis caused by *P. chinensis*, with 4 subjects demonstrating allergic rhinitis, urticaria and bronchial hyperreactivity and 5 subjects (71%) had positive IgG4 antibody levels. Increasing IgG4 titres are often seen after receiving immunotherapy, but the treatment had not been provided. The relevance of this antibody type is not well understood and need to be further investigated. The analysis of the skin-prick tests to *P. chinensis* extract in Korea was positive in all patients with systemic allergic reactions (positive response defined as allergen/histamine wheal size ratio, of 2+ or greater), whereas 23.3% of asymptomatic residents and 2.7% of the controls showed also positive skin prick test results in that area (Cho et al., 2002). The determination of serum-specific IgE levels by ELISA showed significantly higher levels in patients with systemic reactions, as compared to patients with large local reaction. Brown et al. (2003a) reports that 93% of allergic patients to *M. pilosula* volunteers had venom-specific IgE reactivity compared to 22% of the non-allergic controls, but serum IgE analysis had lower sensitivity as compared to the skin prick testing (sensitivity 0.93; specificity 0.78). Patients with anaphylactic reactions to bulldog ant stings (*M. gratioiosa*, *M. ludlowi* and *M. nigriscapa*) had severe symptoms, ranging from mild to severe and clearly life-threatening anaphylaxis, and demonstrated considerable cross-reactivity of IgE binding between bulldog ant venom species (Gilhotra and Brown, 2006).

There are reported anaphylactic reactions to imported fire ant stings with 83 deaths and two near fatal in North America (Rhoades et al., 1989). Moreover fatalities to the *Solenopsis* species fire ants were reported in a 3 month old infant (More et al., 2008) and a one and half year old (Havaladar et al., 2012). The development of anaphylaxis to the sting was followed by a history of anaphylactic reactions to Hymenoptera sting and positive skin prick tests to venom predicted that at least 60% of adults and 20–30% of children will develop anaphylaxis with future stings. Immunotherapy seems to be very effective for at least 4 years and demonstrated by only 3% of re-sting patients developed anaphylactic reactions, and might be

increased after discontinuing therapy, but reported to increase to not more than 10% (Koterba and Greenberger, 2012).

5. Management

The most important aspect in the management of any allergic disorder is allergen avoidance. Treatment decisions are based both on the severity of previous reactions and the risk of future stings. Patients need to be instructed on the importance of avoidance including not disturbing of ant nests using insecticides and wearing shoes while walking outdoors, especially since the stings can occur around the homes in the Asia-Pacific region (Shek et al., 2004). Pest control and elimination of ant nests from home areas should be considered by patients. Immunotherapy to ant stings is not available in many countries in the Asia-Pacific region because there are insufficient data on its efficacy and lack of expert physician. There are reports about double blind, placebo-controlled crossover trials to the feasibility and efficiency of ant VIT (Brown et al., 2003b). Randomly allocated allergy volunteers with clinical symptoms to *M. pilosula* venom received VIT, while the control group received only placebo. In the later group 21 of the 29 patients demonstrated clinical symptoms after sting challenge, with 8 having hypotension, while only one of the VIT treated 23 patients had transient urticaria. After crossover 30 participants from the placebo to the VIT group, only one person reacted to the sting challenge (transient urticaria), demonstrating similar efficiency. In total 22 out of 64 volunteers (34%) exhibited a systemic hypersensitivity reaction to VIT. This trail of VIT show that it is an effective treatment for *M. pilosula* sting anaphylaxis, but there is a risk of systemic reactions during VIT that should be considered where there is immediate access to resuscitation facilities. A double-blinded study of *M. pilosula* venom therapy proved highly effective to 34% of patients with systemic reactions during treatment (Weber, 2010). IFA subcutaneous immunotherapy and WBE is both safe and effective in prevention of IFA subsequent sting anaphylaxis (Stokes et al., 2013; Tankersley et al., 2002). Moreover, VIT is highly effective treatment and prevention of *M. pilosula* sting anaphylaxis as well (Brown et al., 2003b). Although there are no evidences of ant immunotherapies for other species, the samsum ant and *P. chinensis* WBE have been used for allergenic patients (Dib et al., 1995; Kim et al., 2001).

6. Conclusion

There are still very little data available on ant allergy in the Asia-Pacific region despite the diversity of ant species and the unique

components of venom in each group. Especially the JJA and related ants produce pilosulin which is not found in other ant groups. The allergenic proteins Sol i 2 and 4 are only found in the fire ant group with a mixture of complex alkaloids, which are not described in other venoms. There are limited studies on other species such as tropical fire ant, Chinese needle ant, samsun ant and harvester ant. Many allergens of these different species are still unknown and need to be identified for better diagnosis and management. While immunotherapy for JJA and IFA demonstrates high efficiency in patients with a history of severe reactions, more specific therapeutics need to be developed for other ant species of importance in the Asia-Pacific region.

Conflict of interests

The authors declare that they have no conflict of interests.

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