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ARTHROPOD ALLERGY AND PUBLIC HEALTH

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INTRODUCTION

Allergic disease, or simply allergy, is a common disorder which affects approximately 40% of global population (Johansson et al. 2000). It is an allergen-mediated hypersensitivity response, involving diverse immunological mechanisms initiated by specific antibodies or cells (Halliwell et al. 2006). Austrian physician Clemens von Pirquet introduced the term "allergy" almost a century ago in a German medical journal to describe the "altered biological reactivity" of the immune response against allergens in the host (Von Pirquet 1906). With the advent of, and advances in molecular biology, the science of allergy has transformed into a major branch of highly sophisticated human and veterinary medicine (Noli et al. 2013).

In immunological terms, an allergen is an antigen. The allergen itself is a non-toxic, non-invasive protein with the potential to initiate immunogenic type-I hypersensitivity reaction by specific immunoglobulin E responses when inhaled, ingested or injected (Goldsby et al. 2003). Most allergens in their natural state are soluble proteins, which chiefly exhibit proteolysis amongst other types of enzymatic activities (Morgan and Arlian 2006; Jeong et al. 2010). The allergic reaction is induced by production of IgE and cross linking of the high-affinity IgE receptor (*FceRI*) on basophil and mast cell surfaces (Kinet 1990; Aalberse 2000). The allergic potential of an allergen is determined by its critical physiochemical properties, such as membranous, mucosal and epithelial permeability, solubility and stability under varying pH and temperature conditions (Christensen et al. 2008). An allergic reaction is dependent upon the amount of allergen exposure and the consequent aggregation of the receptors (Marshall et al. 1986). Allergy, being an immune-mediated disease, is complex and multifactorial in nature. Evidence suggests that allergic individuals have genetic predisposition (Vercelli 2008; Tan et al. 2012; Kanchan et al. 2021). Key factors affecting the outcome of allergy are a combination of underlying genetic vulnerability and triggering factors, such as immunological dysregulation and environmental influences (Jabbar-Lopez et al. 2020; Kanchan et al. 2021).

The term atopy is derived from the Greek word "atopos", meaning out of place, and is typically associated with IgE-mediated diseases (Kay 2001). Asthma, atopic eczema, dermatitis and allergic rhinitis are the most frequent manifestations of atopy and are amongst the most common global causes of chronic public health problems. Combination of these diseases is called the atopic triad, as shown in Figure 1 (Devereux and Seaton 2005; Vaillant et al. 2020). The immunopathological hallmark of atopy is type 2 helper cell (Th2) infiltration. An exaggerated immunological response elevates serum IgE levels and induces cytokine production by Th2 cells (Lauzon-Joset et al. 2020; Lee et al. 2021). The concentration and duration of allergen exposure, along with the avidity of allergen-specific interactions, determine the influence of Th1 and Th2 cells in the affected tissues (Constant and Bottomly 1997; Rogers and Croft 1999). Atopic allergic diseases are hereditary and often have a family history (Kay 2001). Several loci have been linked to atopy through candidate gene approach. Polymorphisms in the IgE receptor gene (*FceRI-β*) are reportedly associated with severe atopy (Cookson 1999). However, the clinical significance of genetic investigation is unclear, because inheritance of susceptibility genotype does not guarantee allergic phenotype, the environment and lifestyle choices strongly influence disease onset and severity (Noli et al. 2013).

Pakistan is a developing country with a very high burden of both communicable and non-communicable diseases (Sultan and Khan 2013). Although researchers, physicians and healthcare professionals in Pakistan are primarily focusing on infectious diseases, allergenic diseases are mostly ignored. Allergy is a neglected disease in Pakistan and little or incomplete data exists on its prevalence. Patients with allergy symptoms ignore them and neither report nor seek effective treatment (Greiner et al. 2011).

Molecular Mechanisms and Pathophysiology

Allergen molecules have specific epitopes which upon exposure in a susceptible individual are recognized as antigens by the immune system. B-cell surface receptors bind to these antigens, signaling endosomes for endocytosis and subsequent degradation by proteases enzymes into immunogenic peptides (Janeway et al. 2001). MHC bearing Golgi bodies fuses with proteolytic enzymes to form peptide-loading vesicles, which bind with the immunodominant peptide. The endosome moves to the cell surface, transforming the B cell into an antigen presenting cell (APC). Helper T-cells (Th1 and Th2) recognize and bind to these B-cell APCs, activating both the T and B-cells (Kinet 1990; Aalberse 2000). A cytokine cascade of interleukin (IL-3, IL-4, IL-5, IL-9, IL-10 and IL-13) is initiated by the activated Th2, enhancing B-cell growth, proliferation and differentiation into IgE producing plasma cells and memory B-cells. Immune cells such as leukocytes (eosinophils, basophils and neutrophils), mast cells and lymphocytes (T and B-cells) are also attracted to the site of allergic reaction (Romagnani 2000).

The B-cell secreted IgE antibodies circulate in the blood and bind to the surface of acute inflammatory immune cells through high-affinity IgE-specific receptors (fc receptors FcεRI). These IgE antibody-coated cells become sensitized to this specific allergen. The main effector cells involved in acute allergic reactions are basophils and mast cells, chiefly located in the eyes, nose and gut mucosa. Figure 2 illustrates the sequence of type-I hypersensitivity reaction upon further allergen exposure. Sensitized cells are activated by forming a cross-linked complex between the IgE antibodies and fc receptors on their surface. Activated cells release powerful soluble inflammatory chemical mediators (histamine, prostaglandins, chondroitin sulfate, heparin, leukotrienes, interleukins, and cytokines), protease enzymes (cathepsins, chymase, tryptase and carboxypeptidase), lipid mediators (thromboxanes, prostaglandins and leukotrienes) and cytokines (IL-3, IL-4, IL-5, IL-9, IL-10, IL-13 and TNF-fi) through a process called degranulation (Kinet 1990). As a result surrounding tissue undergoes physiological effects, such as nerve stimulation (itchiness and sneezing), mucosal secretion (rhinorrhea and epiphora), smooth muscle contraction (wheeze and dyspnea) and vasodilation (edema and erythema). Allergen concentration and host susceptibility can lead to classical anaphylaxis (Janeway et al. 2001; Arlian 2002).

Arthropod Allergy

Over a million species of arthropods have been described, all of which are important to humans due to their economic, ecological or pathological significance. Arthropods of clinical relevance include vectors, parasites and allergen producers (Yong and Jeong 2009). Arthropod proteins of virtually all species may be potent sources of IgE-mediated allergy in susceptible human populations (Kagen 1990; Kim and Hong 2007). Arthropod allergy and characteristics of their allergens have been extensively studied as a major research discipline in parasitology and medical arthropodology.

In recent decades, a rise in arthropod allergy has been reported which is mostly attributed to household arthropods. This trend may be a consequence of modern human lifestyle and extended periods of indoor activities. Economics, lifestyle choices and environment encourage the growth and multiplication of certain arthropods, such as cockroaches and mites, which results in increased human exposure, leading to sensitization or clinical manifestations (Kim and Hong 2007). Arthropod allergies are reported due to ingestion (shellfish allergy caused by crustaceans), inhalation (aeroallergens of mites, roaches and insects), contact (silk proteins) or injection (hymenopteran and formicidae stings) (Arlian 2002). Types of arthropod allergens are illustrated in Figure 3.

Several allergens identified from arthropods are classified, based on their biological functions and molecular structures (Gaffin and Phipatanakul 2009). More than half of major allergens are lipid and fatty acid binding proteins, calycins and lipocalins found in arthropod fluids and secretions (Mantyjarvi et al. 2000; Trompette et al. 2009).

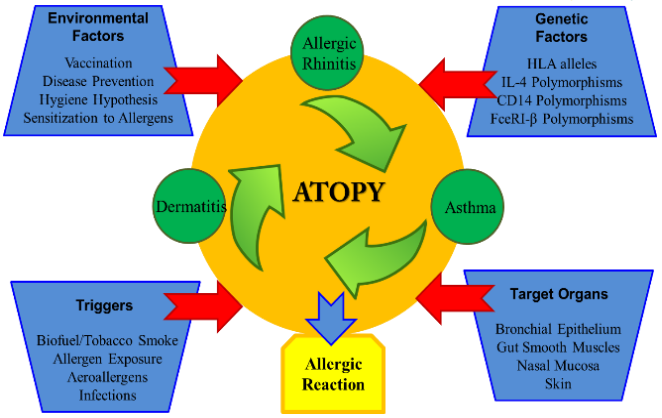

Fig. 1: The atopic triad: Asthma, atopic eczema/dermatitis and allergic rhinitis.

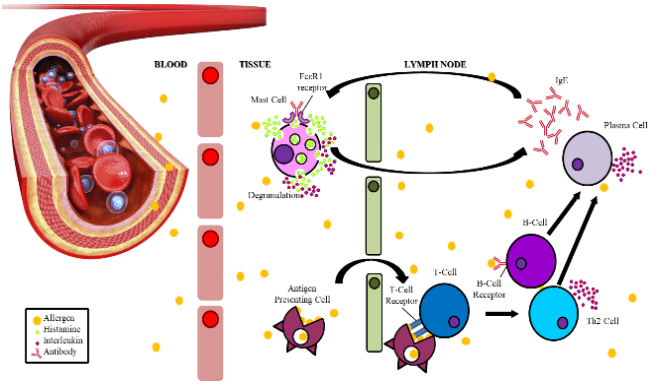

Fig. 2: Acute phase hypersensitivity type-I reaction against an allergen.

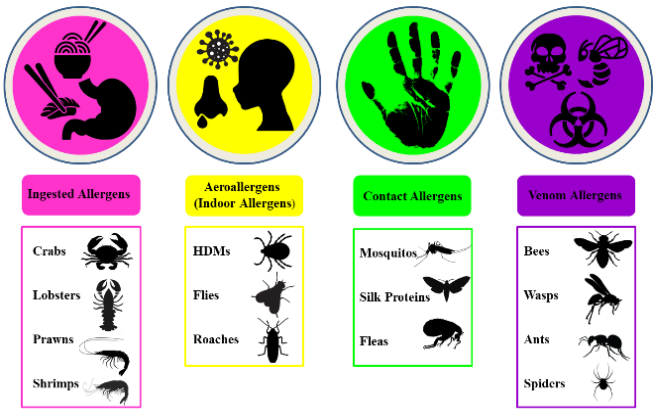

Fig. 3: Types of arthropod allergens.

Evidence suggests that protease activity is also an important allergenic property and is implicated in increased IgE production by direct epithelium damage (Jeong et al. 2006; Chapman et al. 2007). None of the known cockroach allergens exhibit active proteolytic activity, however allergic inflammation is associated with serine proteases found in cockroach extracts (Pomes et al. 2007; Jeong et al. 2008). House dust mite (HDM) allergens are identified as chitinases and have demonstrated an important role in development and mediation of Th2 cell-driven inflammation in asthma (O'Neil et al. 2006). Tropomyosin is a heat stable allergen found in edible arthropods, such as crustaceans (Taylor and Lehrer 1996).

Table 1: Classification of shellfish arthropod species

Phyla	Sub-Phyla	Class	Order	Common name
Arthropoda	Crustacea	Malacostraca	Decapoda	Shrimps (Caridea) Prawns (Penaeidae) Crabs (Brachyura) Lobsters (Nephropidae) Crayfish (Cambarus)
				Spiders Mites
		Arachnida	Araneae	Dust Mites
Arthropoda	Chelicerates	Xiphosura		Horseshoe Crab
Arthropoda	Myriapoda	Chilopoda		Centipedes Millipedes

Table 2: List of identified and characterized shellfish allergens (Radauer et al. 2008)

Allergen	Molecular Weight	Heat Stability	IgE Binding	Route of Exposure	Physiological Function
Tropomyosin	34–38 kDa	Highly heat stable	Reactive	Ingestion Inhalation	Actin binding Regulation of myosin and troponin
Arginine Kinase	40–45 kDa	Labile	Reactive	Ingestion Inhalation	Catalyst Reversible transfer ATP phosphoryl group to arginine
Myosin Light Chain	17–20 kDa	Stable	Reactive	Ingestion	Regulation of smooth muscle contraction in the presence of MLC kinase
Sarcoplasmic calcium Binding Protein	20–25 kDa	Stable	Reactive	Ingestion	Calcium buffer Cytosolic calcium (Ca^{2+}) binding Regulation of calcium based signaling
Troponin C	20–21 kDa	Unknown	Reactive	Ingestion	Muscle contraction Calcium binding Regulation of actin and myosin
Triosephosphate Isomerase	28 kDa	Labile	Reactive	Ingestion Inhalation	Key glycolysis enzyme Catalyst Conversion of dihydroxyacetone phosphate to glyceraldehyde 3-phosphate

Ingested Arthropod Allergens

Seafood is an important part of human diet. Its consumption has increased in recent years due to growing international trade and distribution of marine products across many countries. However, seafood allergy is one of the most prevalent causes of food induced anaphylaxis in the world. It is more than twice as prevalent as peanut allergy (Sicherer et al. 2004). Shellfish are a common cause of allergic anaphylaxis, affecting children and adults of all ages however, it is 5 times more prevalent amongst adults than children (Lopata et al. 2016; Sicherer and Sampson 2010). Studies have shown that allergic reaction in sensitized individuals can not only be elicited by shellfish ingestion but through air-borne shellfish allergens as well. This is especially evident from occupational risk studies (Gautrin et al. 2010; Bonlokke et al. 2012; Kamath et al. 2014).

Shellfish and Crustacean Allergens

Shellfish are classified into one chordate and two invertebrate groups, Mollusca and Arthropoda (crustaceans). Phylogenetically, arthropod shellfish or crustaceans are related to arachnids and insects (Afzaal et al. 2016). Classification of arthropod shellfish species is shown in Table 1. More than 50,000 crustacean species have been described (Chan 1998). Many such varieties are used for human consumption, either cooked or raw. Shellfish allergy is the most prevalent of the eight common food allergens inculpated in 90% type-I hypersensitivity reactions to food (Rona et al. 2007). Majority (62%) of arthropod shellfish allergies are attributed to prawns, followed by crabs and lobsters (Sicherer et al. 2004). Six major shellfish allergens have been identified from crustaceans (Table 2) and are registered in the International Union of Immunological Societies (IUIS) Allergen Database (www.allergen.org) (Radauer et al. 2008). These allergenic proteins are highly water soluble light molecules with the ability to maintain stability at high heat and have an acidic isoelectric point (Sun and Lopata 2010). The list of characterized crustacean allergens is shown in Table 3.

Prevalence and Epidemiology

Approximately 2% of global population is affected by shellfish allergy. It has a particular impact in the Asia-Pacific region, where seafood consumption is the highest in the world (Lee et al. 2012). After Japan and China, America is the third largest seafood consumer in the world (Sicherer et al. 2004). Overall prevalence of shellfish allergy in the western world (Canada, USA and Europe) is estimated to be 0.6% (Rona et al. 2007). Iceland has the highest seafood consumption rates in Europe, followed by Portugal, Norway, Spain, France, United Kingdom and Germany (Lopata et al. 2010).

While majority of allergen studies in Pakistan are focused on aeroallergens such as pollen and HDMs, shellfish allergies are mostly ignored. A recent local study involving a small sample (n=149) has reported shellfish allergy as the most prevalent of the tested food allergens, implicating crabs (70%; n=39) and prawns (46%; n=26) (Hussain et al. 2020). However, clinical record has revealed that approximately 90% allergic patients suffered from aeroallergen sensitization, whereas only 10% had food allergies (Hussain et al. 2019). This may be due to lower seafood consumption rates in Pakistan. According to the Food and Agriculture Organization (FAO) food balance sheet (FBS) for South East Asia, Pakistan ranked the lowest in seafood consumption rates (0.9 kg per capita per year) in 2015. This figure was even less in 2011 (0.6 kg per capita). Even though seafood in Pakistan is consumed in coastal provinces of Sindh (1.6 kg) and Balochistan (2.4 kg), its consumption is recorded to be very less in Punjab (0.2 kg) and even less in the Northern regions of Khyber Pakhtunkhwa (0.05 kg) (FAO-FBS 2015 online resource). Some common shellfish species found in Pakistan are shown in Figure 4.

Clinical Manifestations

Allergic reaction to ingested arthropod allergens is symptomatically similar to any of the eight major allergic reactions. The severity of reaction may vary from tolerable to fatal. Atopic individuals are at a higher risk of developing anaphylactic reaction to food allergens. Itching and angioedema of the lips, mouth and pharynx is usually immediate i.e., within 2 hours of consumption, however late-phase reaction may take up to 8 hours (Villacis et al. 2006). Respiratory distress, particularly oral allergy syndrome, is experienced due to ingested allergens like crustacean (Dohi et al. 1991). Typical type-I hypersensitivity reaction due to ingested allergens are given in Table 4.

Table 3: Characterized crustacean allergens (IUIS Allergen Nomenclature)

		Shellfish Species	Common names	Tropo-myosin	Arginine Kinase	Myosin Light Chain 1 and 2	Sarcoplasmic Calcium Binding Protein	Troponin C, Troponin I	Triose-phosphate somerase
Crusta-ceans	Shrimp	*Penaeus monodon*	Asian Tiger Shrimp	Pen m 1	Pen m 2	Pen m 3	Pen m 4	Pen m 6	Cra c 8
		Penaeus aztecus	Brown Shrimp	Pen a 1	-	-	-	-	-
		Crangon crangon	Common Shrimp	Cra c 1	Cra c 2	Cra c 5	Cra c 4	Cra c 6	-
		Litopenaeus vannamei	Vannamei Shrimp	Lit v 1	Lit v 2	Lit v 3	Lit v 4	-	-
		Pandalus borealis	Pink Shrimp	Pan b 1	-	-	-	-	-
		Metapenaeus ensis	Sand Shrimp	Met e 1	-	-	-	-	-
		Archaeopotamobius sibiriensis	ND	-	-	-	-	-	Arc s 8
		Machrobrachium rosenbergii	Giant Fresh Water Shrimp	Mac ro 1	-	-	-	-	-
	Prawn	*Melicertus latisulcatus*	King Prawns	Mel l 1	-	-	-	-	-
		Penaeus indicus	Indian White Prawn	Pen i 1	-	-	-	-	-
	Crab	*Charybdis feriatus*	Crucifix Crab	Cha f 1	-	-	-	-	-
		Portunus pelagicus	Blue Swimmer Crab	Por p 1	-	-	-	-	-
	Lobster	*Homarus americanus*	American Lobster	Hom a 1	-	Hom a 3	-	Hom a 6	-
		Panulirus stimpsonii	Spiny Lobster	Pan s 1	-	-	-	-	-
	Crayfish	*Pontastacus leptodactylus*	Narrow-Clawed Crayfish	Pon i 1	-	-	-	-	-

*Allergens nomenclature is registered with International Union of Immunological Societies (www.allergen.org).

Table 4: Type-I hypersensitivity reaction due to ingested allergens

Time	Severity	Symptoms	
Immediate	Mild	–	Facial, mouth or tongue tingling
		–	Urticaria, itching or eczema
		–	Angioedema of the face, lips, tongue or throat
Within 1 to 2 hours	Tolerable	–	Wheeze or nasal congestion
		–	Breathing difficulty
		–	Nausea or vomiting
		–	Abdominal pain or diarrhea
Within 8 hours	Anaphylaxis	–	Airway constriction manifesting as a throat lump
		–	Severe drop in blood pressure and vitals
		–	Lightheadedness, dizziness or loss of consciousness
Chronic sensitization	Complication	–	Asthma exacerbations
		–	Extreme sensitivity to trace amounts of allergen
		–	History of food-induced anaphylaxis

Prevention and Management

As with all types of allergies, prevention of ingested allergens such as shellfish allergy is to avoid seafood and shellfish products. Even trace amounts may result in severe immunological reaction. Shellfish is rarely a hidden food ingredient, which makes it easier to avoid when dinning out. However, seafood flavoring, shellfish stock, oils and cross-contamination through pans and utensils pose a high risk to allergic individuals. Further, cross-contamination may occur in markets, food stores, factory packaged materials where shellfish are prepared, processed or stored. Some individuals may suffer an allergic reaction due to air-borne or even through contact with shellfish allergens. A medical alert bracelet worn at all times, especially when eating out, is also a good management practice.

Arthropod Aeroallergens (Indoor Allergens)

Arthropod derived aeroallergens are potent inducers of respiratory inflammation. Arthropod secretory or excretory materials induce IgE responses. Inhalation of environmental arthropod allergens (house dust mites, cockroaches, moths and butterflies) may induce persistent airway diseases such as asthma (Kang and Chang 1985). Population fluctuations in indoor arthropods are usually very slight, which consequently results in perennial allergy instead of seasonal allergy unlike pollen and other aeroallergens (Yong and Jeong 2009; Calderón et al. 2015). Although true allergens such as Anisakis simplex antigen (Ani s 1) have been identified (*Anisakis* spp. larvae), most arthropod-derived materials implicated in increased IgE levels are considered allergens (Ibarrola et al. 2008).

House Dust Mites (HDMs) Allergens

Dust mites are taxonomically classified in the class Arachnida, which makes them phylogenetic relatives of scorpions, spiders and centipedes (Colloff 1998; Esch et al. 2001). More than 40 HDM species have been described. The most common of these are shown in Figure 5. HDMs are medically important due to their role in allergy and atopy (Dhaliwal et al. 2021). Allergic asthma and rhinitis are associated with HDMs prevalence (Terreehorst et al. 2002; Li et al. 2013). HDM larvae have 3 pairs of legs, whereas adults have an additional pair of legs, totaling in 4 pairs. They are mostly found in human dwellings and indoor environments, such as settled dust, pillows, blankets, mattresses and bedding. Food sources include human skin scales, cotton fibers, wood, paper and synthetic materials. Water is absorbed from air. Most favorable growth and sustainability conditions include 23-30ºC temperature and 80-90% relative humidity, which makes HDM infestations, particularly destructive in tropical and sub-tropical coastal cities (Guerrant et al. 2006).

Mite-derived allergens enter the respiratory track through inhalation. They vary in size, ranging from very small (1.1-4.7 µm) to larger (>4.7 µm) particles. Large particles, even in smaller quantities, can elicit more substantial early-phase immune response (Casset et al. 2006), however smaller particles can penetrate far deeper into the lungs (Custovic et al. 1999). HDM allergens manifest as rhinitis, bronchial asthma, and rarely-conjunctivitis. To date more than 24 groups of HDM allergenic proteins have been identified and characterized (Table 5). HDM allergens are potent antigens, which orchestrate combined effects of both the innate and the adaptive immune responses. They distort the immune response by mimicking virulent pathogen-associated molecular patterns and activating multiple routes (Wang 2013). They may initiate IgE independent activation of mast cells, causing direct damage to the epithelial cells of the respiratory tract (Takai and Ikeda 2011). Whereas, HDM immunogenic components such as epitopes and proteases along with structural polysaccharides derived from HDM ligands and exoskeleton cause IgE-dependent allergic responses through $CD4^+$ and T_H^2 cell activation (Jacquet 2013; Wang 2013). This combined effect of the immune responses is the therapeutic barrier marring clinical efficacy.

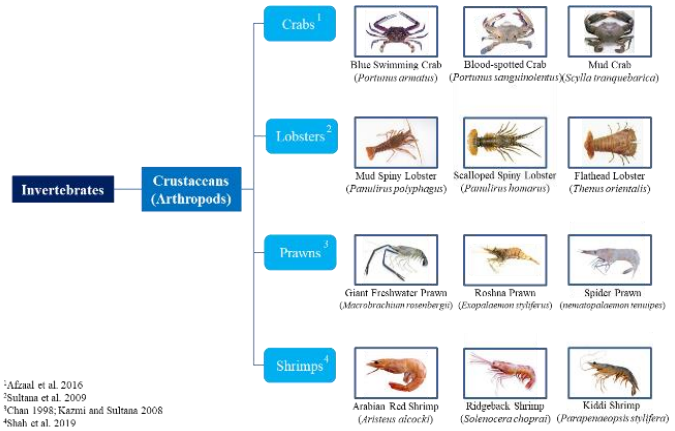

Fig. 4: Common commercial shellfish species from Pakistan.

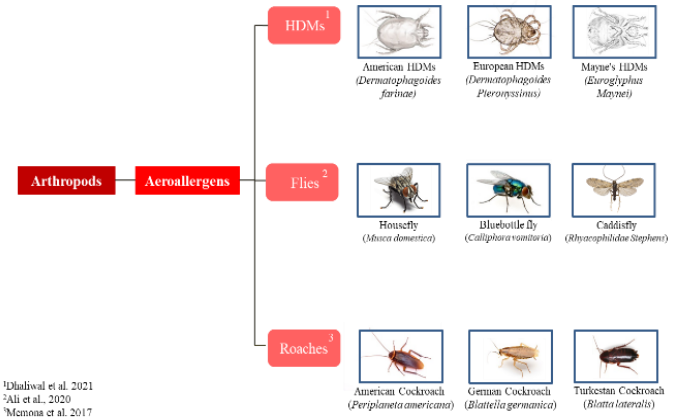

Fig. 5: Common aeroallergen producing arthropod species in Pakistan.

Prevalence and Epidemiology

It is estimated that 65 - 130 million persons or 1-2% of the global population is affected by HDMs (Colloff 1998). Three HDM species, *Dermatophagoides pteronyssinus*,

Dermatophagoides farinae and *Euroglyphus maynei,* are the most common dust mites by density and species prevalence (Arlian et al. 1992). Regional climate influences HDMs population density, HDM allergen being highest in summer and lower during winter. Indoor microclimate plays a dramatically crucial role. Air-conditioning has been reported to significantly reduce HDM allergens (Lintner and Brame 1993). However, geographical variations in HDM species dominance are strong indicators of specialist adaptation (Thomas 2010). Prevalence of HDM allergy is dependent on the density of exposure. Settled dust provides a detrital habitat for HDMs and serves as a reservoir of organic macromolecules, such as cellulose (textile fibers), keratin (human skin scales) and chitin (fungal hyphae and mite cuticles), along with other HDM dietary sources pollen, bacteria and microscopic spores (Calderón et al. 2015). It has been noted that HDM densities were decreased in houses furnished with new carpets, curtains and mattresses (Simpson et al. 2002).

Clinical Manifestations

HDM allergen is perennial, since HDM inhabit mattresses, bedcovers, blankets and pillows (Yong and Jeong 2009; Calderón et al. 2015). This causes year-round allergy symptoms, which mostly occur during late night or early morning. The most common HDM allergens are Der p 1, Der p 2, Der p 23, Der f 1 and Der f 2. These allergens target CD23 and CD25 triggering release of immunoglobulin E (Chapman et al. 2007). Catalytic inactivation of alpha antitrypsin by the most potent HDM allergen Der p 1, makes the lower respiratory tract vulnerable to proteinases mediated damage causing airway inflammation, which is extremely devastating in asthmatics (Wang et al. 2021).

Table 5: HDM allergen groups and their immunological roles (IUIS Allergen Nomenclature)

Allergen Group	Identified Allergens	Molecular Category	Molecular Weight	Quantitative Allergenicity	Species	Role in Immunity
1.	Blo t 1 Der f 1 Der m 1 Der p 1 Der s 1 Eur m 1 Pso o 1 Sar s 1	Cysteine Protease	25 kDa	80% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides farina* *Dermatophagoides microceras* *Dermatophagoides pteronyssinus* *Dermatophagoides siboney* *Euroglyphus maynei* *Psoroptes ovis* *Sardinops sagax*	– Production of chemokines, cytokines and growth factors – Production and promotion of pro-T_H^2 polarization – Inflammatory cell recruitment – Airway remodeling – Disruption of epithelial junctions to increase permeability – Degranulation of mast cells and eosinophils – Fibroblast maturation – Proliferation of smooth muscles
2.	Aca s 2 Ale o 2 Blo t 2 Der f 2 Der p 2 Der s 2 Eur m 2 Gly d 2 Lep d 2 Pso o 2 Sui m 2 Tyr p 2	MD-2–like lipid-binding protein Niemann-Pick C2 homologue	14 kDa	80% IgE binding frequency	*Acarus siro* *Anacardium occidentale* *Blomia tropicalis* *Dermatophagoides farina* *Dermatophagoides pteronyssinus* *Dermatophagoides siboney* *Euroglyphus maynei* *Glycyphagus domesticus* *Lepidoglyphus destructor* *Psoroptes ovis* *Suidasia medanensis* *Tyrophagus putrescentiae*	– Production of chemokines and cytokines – Promotion of T_H^2 polarization – Inflammatory cell recruitment – Molecular mimicry of MD-2 or NPC2-like proteins – Activation of TLR2 and TLR4 on airway epithelium – C-Type Lectin Receptor binding on dendritic cells by glycosylation – Release of TNF-α
3.	Blo t 3 Der f 3 Der p 3 Der s 3 Eur m 3 Gly d 3 Lep d 3 Sar s 3 Tyr p 3	Trypsin-like serine protease	25 kDa	16% to 100% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides farinae* *Dermatophagoides pteronyssinus* *Dermatophagoides siboney* *Euroglyphus maynei* *Glycyphagus domesticus* *Lepidoglyphus destructor* *Sarcoptes scabiei* *Tyrophagus putrescentiae*	– Production of chemokines, cytokines and growth factors – Production and promotion of pro-T_H^2 polarization – Inflammatory cell recruitment – Airway remodeling – Disruption of epithelial junctions to increase permeability – Degranulation of mast cells and eosinophils

						– Fibroblast maturation – Proliferation of smooth muscles
4.	Blo t 4 Der f 4 Der p 4 Eur m 4	α-Amylase	56 kDa	40% to 46% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides farinae* *Dermatophagoides pteronyssinus* *Euroglyphus maynei*	Unknown
5.	Blo t 5 Der f 5 Der p 5 Gly d 5 Lep d 5	Lipid-binding protein	15 kDa	50% to 70% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides farinae* *Dermatophagoides pteronyssinus* *Glycyphagus domesticus* *Lepidoglyphus destructor*	– Production of chemokines, cytokines and growth factors – Production and promotion of pro-T_H^2 polarization – Inflammatory cell recruitment – Stimulation of innate immunity by hydrophobic ligand binding – Activation of Toll-Like Receptor (TLR) Signaling Pathways
6.	Blo t 6 Der f 6 Der p 6	Chymotrypsin-like serine protease	25 kDa	40% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides farinae* *Dermatophagoides pteronyssinus*	– Production of chemokines, cytokines and growth factors – Production and promotion of pro-T_H^2 polarization – Inflammatory cell recruitment – Airway remodeling – Disruption of epithelial junctions to increase permeability – Degranulation of mast cells and eosinophils – Fibroblast maturation – Proliferation of smooth muscles
7.	Blo t 7 Der f 7 Der p 7 Gly d 7 Lep d 7	Lipid-binding protein	24 kDa	50% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides farinae* *Dermatophagoides pteronyssinus* *Glycyphagus domesticus* *Lepidoglyphus destructor*	– Production and promotion of pro-T_H^2 polarization – Activation of Toll-Like Receptor (TLR) Signaling Pathways – Stimulation of innate immunity – Structural similarity to lipopolysaccharides (LPS)-binding proteins – Acts as ligand for other bacterial ligands
8.	Blo t 8 Der p 8 Gly d 8 Lep d 8 Pso o 8 Sar s 8	Glutathione-S-transferase	26 kDa	20% to 40% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides pteronyssinus* *Glycyphagus domesticus* *Lepidoglyphus destructor* *Psoroptes ovis* *Sarcoptes scabiei*	Unknown
9.	Blo t 9 Der f 9 Der p 9	Collagenolytic-like serine protease	29 kDa	90% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides farinae* *Dermatophagoides pteronyssinus*	– Production of chemokines, cytokines and growth factors – Disruption of epithelial junctions to increase permeability – Production and promotion of pro-T_H^2 polarization – Inflammatory cell recruitment – Airway remodeling – Degranulation of mast cells and eosinophils

						– Production of chemokines, cytokines and growth factors
10.	Blo t 10 Der f 10 Der g 10 Der p 10 Gly d 10 Lep d 10 Pso o 10 Tyr p 10	Tropomyosin	35 kDa	50% to 95% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides farinae* *Dermanyssus gallinae* *Dermatophagoides pteronyssinus* *Glycyphagus domesticus* *Lepidoglyphus destructor* *Psoroptes ovis* *Tyrophagus putrescentiae*	Unknown
11.	Blo t 11 Der f 11 Der p 11 Pso o 11 Sar s 11	Paramyosin	100 kDa	80% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides farinae* *Dermatophagoides pteronyssinus* *Psoroptes ovis* *Sarcoptes scabiei*	Unknown
12.	Blo t 12 Der p 12 Lep d 12	Chitinase	14 kDa	50% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides pteronyssinus* *Lepidoglyphus destructor*	Unknown
13.	Aca s 13 Blo t 13 Der f 13 Gly d 13 Lep d 13 Try p 13	Lipocalin Fatty acid binding protein	15 kDa	10% to 20% IgE binding frequency	*Acarus siro* *Blomia tropicalis* *Dermatophagoides farinae* *Glycyphagus domesticus* *Lepidoglyphus destructor* *Tyrophagus putrescentiae*	– Activation of Toll-Like Receptor (TLR) Signaling Pathways – TLR and T_H^2 cells polarization
14.	Blo t 14 Der f 14 Der p 14 Eur m 14 Pso o 14 Sar s 14	Vitellogenin/ apolipophorin-like	177 kDa	90% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides farinae* *Dermatophagoides pteronyssinus* *Euroglyphus maynei* *Psoroptes ovis* *Sarcoptes scabiei*	– Activation of Toll-Like Receptor (TLR) Signaling Pathways – TLR and T_H^2 cells polarization – IL-4 and IL-13 production
15.	Der f 15 Der p 15	Chitinase	63 kDa	70% IgE binding frequency	*Dermatophagoides farinae* *Dermatophagoides pteronyssinus*	– Mostly unknown – T_H^2 cells polarization
16.	Der f 16	Gelsolin	55 kDa	50% IgE binding frequency	*Dermatophagoides farinae*	Unknown
17.	Der f 17	Calcium binding EF protein	30 kDa	35% IgE binding frequency	*Dermatophagoides farinae*	Unknown
18.	Blo t 19 Der f 18 Der p 18	Chitinase-like protein	60 kDa	55% IgE binding frequency	*Blomia tropicalis* *Dermatophagoides farinae* *Dermatophagoides pteronyssinus*	– Mostly unknown – T_H^2 cells polarization
19.	Blo t 19	Antimicrobial peptide	7 kDa	10% IgE binding frequency	*Blomia tropicalis*	Unknown
20.	Der p 20	Arginine kinase	20 kDa	-	*Dermatophagoides pteronyssinus*	Unknown
21.	Blo t 21 Der p 21	Lipid-binding protein	-	-	*Dermatophagoides pteronyssinus*	– Mostly unknown – T_H^2 cells polarization
22.	Der f 22	Lipid-binding protein	-	-	*Dermatophagoides farinae*	Unknown
23.	Der p 23	Chitin-binding protein	14 kDa	-	*Dermatophagoides pteronyssinus*	Unknown
24.	Der f 24	Troponin C	18 kDa	-	*Dermatophagoides farinae*	Unknown
25.	-	α-tubulin	51 kDa	-	*Lepidoglyphus destructor* *Tyrophagus putrescentiae*	Unknown
26.	-	Heat shock protein 70	70 kDa	-	*Blomia tropicalis* *Dermatophagoides farinae*	Unknown

*Allergens nomenclature is registered with International Union of Immunological Societies (www.allergen.org)

Typical symptoms due to HDM allergy include coughing, sneezing, nasal or oral itchiness, shortness of breath, allergic conjunctivitis, rhinorrhea and lethargy. HDM mediated asthma may result in tightness or discomfort in chest, wheezing and dyspnea (Huss et al. 2001; Bourdin et al. 2009; Shafique et al. 2018). Cross reactivity due to HDM allergen sensitivity may also result in development of allergic sensitization to mollusks and shellfish.

Prevention and Management

Prevention is the most effective intervention against HDM allergy. Household bedding, mattresses, pillow etc. may be encased in plastic to prevent penetration. Infested items, heavy fabric drapes and carpeting should either be removed, periodically replaced or washed weekly in hot water (55-60°C). Vacuum cleaning should be the preferred method of cleaning over dry dusting.

Non-Biting Flies

Flies are a common environmental occurrence. They are not only responsible for communicating parasites and infectious diseases as vectors for various viral, bacterial, protozoan, and fungal pathogens (Khamesipour et al. 2018) but are also implicated in aeroallergen induced allergy (Sgambato et al. 1987). Urticaria, rhinitis, erythema, conjunctivitis and respiratory difficulties have been associated with exposure to flies and their maggots (Kino et al. 1987; Martinez et al. 1997). Occupational allergy due to flies is affected by several factors, such as availability of shelter, water and nutritional sources (Tee et al. 1985; Kraut et al. 1994). Some common biting and non-biting flies implicated in allergic reactions are shown in Figure 6.

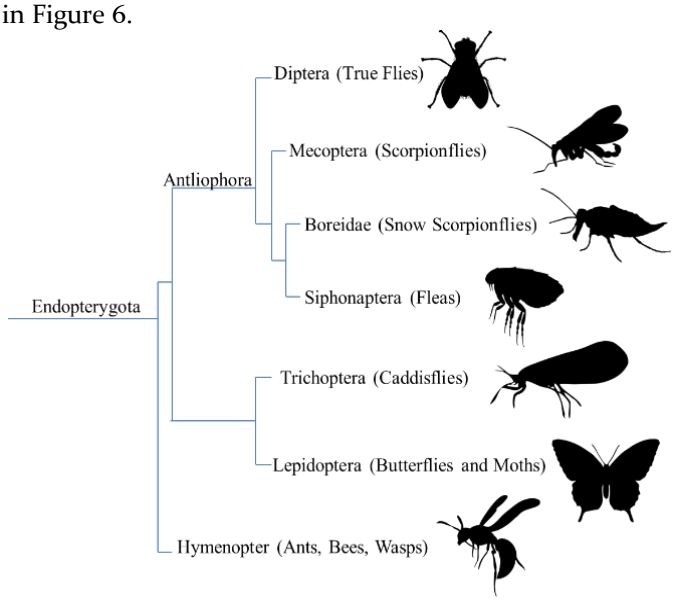

Fig. 6: Cladogram of biting and non-biting flies.

Common Housefly (*Musca domestica*)

Houseflies belong to the order Diptera, and are known as true flies. Although the common housefly (*Musca domestica*) is recognized as a cause of nasal allergy for many years (Jamieson 1938; Tee et al. 1985), relatively fewer incidences are reported as case studies. Housefly emanated particles (wings and body sheddings, follicles, excreta) and body secretions (saliva) are potent IgE-mediated aeroallergens responsible for asthma exacerbations, especially in children (Lierl et al. 1994). Previous studies have confirmed high-affinity IgE cross reactions between the sera of sensitized individuals against protein molecules from housefly extracts (Baldo and Panzani 1988; Martinez et al. 1997). Occupational allergy to houseflies has been reported in infested barn workers (Wahl and Fraedrich 1997), farmers (Focke et al. 2003) and pharmaceutical industry workers engaged in fly breeding (Tee et al. 1985; Tas et al. 2007).

Bluebottle Fly (*Calliphora vomitoria*)

The bluebottle fly (*Calliphora vomitoria*) is twice the size of a common housefly (Whitworth 2006). It is named so because of characteristic black and bright metallic blue abdominal markings. Wings of this fly are transparent, body and legs are covered with dark hair-like bristles, while antennae are short and club-shaped (Chinery and Legrand 2012). *Calliphora* maggots are used in live bait fishing. Bluebottle fly allergy is mostly reported by fishing bait breeders (Pazzaglia et al. 2003), occupational and recreational fishermen (Félix-Toledo et al. 2005). Symptoms typically appear within an hour of exposure, resulting in itchiness of the hands which extends to face and neck, accompanied by urticaria and rhinoconjunctivitis. Respiratory difficulties, such as congestion in chest and wheeze, appear after 6-8 hours and progressively worsen with time (Stockley et al. 1982; Siracusa et al. 2003). IgE-immunoblotting has revealed protein bands of 14, 28, 40, 46, 73 and kDa weights (Tideman and Elberink 2009; Porcel Carreño et al. 2013). *Calliphora* allergy prevalence has not been extensively investigated.

Caddis Fly (*Rhyacophilidae Stephens*)

Rhyacophilidae are free and parasitic insects. Adult flies appear like moths, since they are closely related to the Lepidoptera. They have bristly and hairy membranous wings. Larvae use silk to encase themselves as pupae (Wiggins 2004; Ali et al. 2020). Investigation of caddis fly extracts has revealed a spectrum of allergenically active low molecular weight proteins (Shulman et al. 1962; Rapp et al. 1962). Post exposure symptoms include epiphora, rhinorrhea, cough, wheeze, and shortness of breath. Incidences of hypersensitivity increase during summer season when new flies are hatched. Power plant managing workforce has been extensively studied in relation to occupational allergy to caddis flies. Caddis flies are attracted to station lights, water, nutritional sources and shelter due to human inhabitation. Adult caddisflies are attracted to both UV and visible spectrums (Kimura and Kuranishi 2020). These flies are sucked into and pulverised by the power turbines and dispersed as aeroallergens (Kraut et al. 1994; Miedinger et al. 2010; McNulty and Divekar 2017). A recent study has reported that professional cleaning workers exhibit airway inflammation and hypersensativity to caddis fly allergens (Lima et al. 2017). Skin prick tests (SPTs) invoked 60% positive results against laboratory prepared caddis fly antigen (LCFA) collected from power plant sites and 39% positive results from commercial caddis fly antigen (CCFA) (Kraut et al. 1994).

Roaches

Cockroaches are primitive but common Neopteran insects, having global distribution. Cockroaches don't have any specialized adaptations, apart from chewing mouthparts called mandibles, allowing them to feed on a great variety of nutritional sources alongside human foods such as starches (paper, leather, glue), fiber (clothing), organic debris (shedding, hair follicles, skin flakes) and other dead insects (Bell 1982). Of the total 4,600 cockroach species described so far, only 50 are considered pestilence

Table 6: Cockroach allergens and their biological roles (IUIS Allergen Nomenclature)

	Identified Allergens	Molecular Category	Molecular Weight	Species	IgE Prevalence	Biological Role
1.	Per a 1	Nitrile-Specifier	45 kDa	*Periplaneta americana*	9-100%	Microvilli-Like Protein with unknown function
	Per a 2	Aspartic Protease-Like	42 kDa		81%	Inactive
	Per a 3	Arylphorins	72 kDa		26-95%	Arthropod Hemocyanins
	Per a 5	Glutathione S-Transferase	23 kDa		25%	Protective enzyme against oxidative damage and insecticides
	Per a 6	Troponin C	36 kDa		14%	Calcium (Ca^{2+}) binding
	Per a 7	Tropomyosin	33 kDa		13-54%	Reduction of IL-12 and TLR9 expression in mastocytoma cells
	Per a 9	Arginine Kinase	43 kDa		80-100%	Unknown
	Per a 10	Serine Protease	28 kDa		82%	Unknown
	Per a 11	Alpha-Amylase	55 kDa		83%	Unknown
	Per a 12	Chitinase	45 kDa		64%	Unknown
	Per a 13	Glyceraldehyde-3-Phosphate Dehydrogenase	17 kDa		*N.R.	Unknown
2.	Bla g 1	Nitrile Specifier	46 kDa	*Blattella germanica*	20-40%	Microvilli-like protein with unknown function
	Bla g 2	Aspartic Protease	36 kDa		40-70%	Binding protein
	Bla g 3	Hemocyanin, Arylphorins	78.9 kDa		*N.R.	Arthropod Hemocyanins
	Bla g 4	Calycin, Lipocalin	21 kDa		17-40%	Unknown function
	Bla g 5	Glutathione S-Transferase	23 kDa		35-68%	Protective enzyme against oxidative damage and insecticides
	Bla g 6	Troponin C	21 kDa		14%	Calcium (Ca^{2+}) binding
	Bla g 7	Tropomyosin	33 kDa		18%	Unknown
	Bla g 8	Light Chain Myosin	21 kDa		*N.R.	Unknown
	Bla g 9	Arginine Kinase	40 kDa		*N.R.	Unknown
	Bla g 11	Alpha-Amylase	57 kDa		*N.R.	Unknown
	Bla g 12	Chitinase	58 kDa		*N.R.	Unknown

*Not reported.

associated with human dwellings (Roth and Willis 1952; Cornwell 1968). Five of the most frequently occurring cockroach pests are the American cockroach (*Periplaneta americana*), German cockroach (*Blattella germanica*), Asian cockroach (*Blattella asahinai*), Oriental cockroach (*Blatta orientalis*) and Turkestan cockroach (*Blatta lateralis*) (Helm et al. 1990; Kang et al. 1996; Memona et al. 2017). Cockroaches are not only vectors of infectious diseases and parasites (Koehler et al. 1990), but allergens derived from cockroach secretions, saliva, excreta, exoskeletons, egg casings and dead bodies are source of powerful aeroallergens implicated in allergic reactions (Lehrer et al. 1991; Arruda and Chapman 2001). Allergic rhinitis, eczema and asthma are amongst the most prevalent chronic disorders in the world, especially in children. An alarming increase in disease incidence and economic burden has been observed in the past few decades (Beasley et al. 2000; Fineman 2002). Genetic variability of a population is not as rapid as environmental variations, which makes aeroallergens largely responsible for allergic diseases (Sears et al. 1989; Sporik et al. 1990).

Particles bearing cockroach allergens are heavy and settle rapidly, becoming air-borne only when disturbed (de Blay et al. 1997). Various investigative studies have detected clinically significant cockroach allergen concentrations in settled dust in kitchen surfaces, lounges, libraries, gymnasiums, cafeterias, hallways, offices, mattresses and floors (Sarpong et al. 1997). Some closely related cockroach species cause cross reactivity due to their similarities. Per a 1 (*Periplaneta americana*) and Bla g 1 (*Blattella germanica*) allergens show cross-reactivity with female *Anopheles gambiae* mosquitoes, with 30% homology (Melen et al. 1999). Other proteins from these two species show moderate homology with other allergenic arthropods, including glutathioneS-transferase of dustmites and other insects, and tropomyosins of shellfish and dust mites (Reese et al. 1999). List of 3 most prevalent cockroach species is given in Table 6.

Prevalence and Epidemiology

Cockroach allergy has been attributed to both genetic and environmental factors (Sohn and Kim 2012). Socioeconomic factors and population density are also important factors (Alp et al. 2001; Leaderer et al. 2002; Mendy et al. 2020). Earliest clinical investigations have implicated cockroach allergen sensitization in 40% asthmatics (Bernton and Brown 1964; Kang et al. 1979). A study in Korea found cockroach infestations in 62% of investigated homes in Seoul. Four species were discovered, *Blattella germanica* (36.2%), *Periplaneta americana* (33.3%), Periplaneta japonica (1.1%) and *Periplaneta Fulginosa* (1.7%) (Lee 1998). Immunological investigations against cockroach extracts in Korean population have revealed 18.7% SPT positivity, elevated IgE levels and 37.5% bronchial constriction (Lee et al. 1993).

Mounting evidence has suggested that cockroach allergen sensitized patients are exposed to cockroach allergens in their own homes (Call et al. 1992; Gelber et al. 1993; Chapman et al. 1996). Cockroach infestations are a major problem in inner city areas and schools, where allergen

levels are clinically significant (Call et al. 1992; Sarpong et al. 1997; Wang et al. 2009). In United States, 36.8% children living in inner city areas were allergic to cockroaches (Rosenstreich et al. 1997). Development of wheeze in one year old children in metropolitan Boston was significantly associated with exposure to cockroach allergens during the first 3 months of their life (Gold et al. 1999; Donohue et al. 2008). Although suburban houses have relatively lower allergens, however 30% suburban and middle-class homes showed detectable levels of cockroach allergens (Gaffin and Phipatanakul 2009). Improved garbage disposal systems and frequent use of pesticides may have contributed to relatively decreased infestation rates (Lee et al. 1993). Cockroach extermination, along with frequent and through cleaning in homes, schools and restaurants, can reduce allergens to clinically insignificant or even undetectable levels (Liccardi et al. 2000; Eggleston and Arruda 2001).

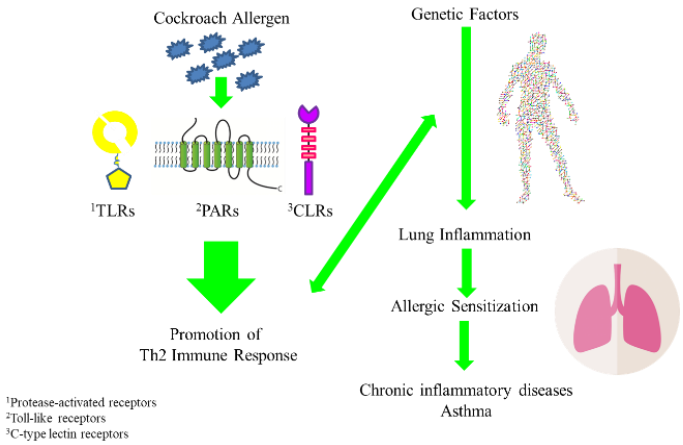

Fig. 7: Mechanism illustrating cockroach allergen-induced allergic sensitization (Gao 2012).

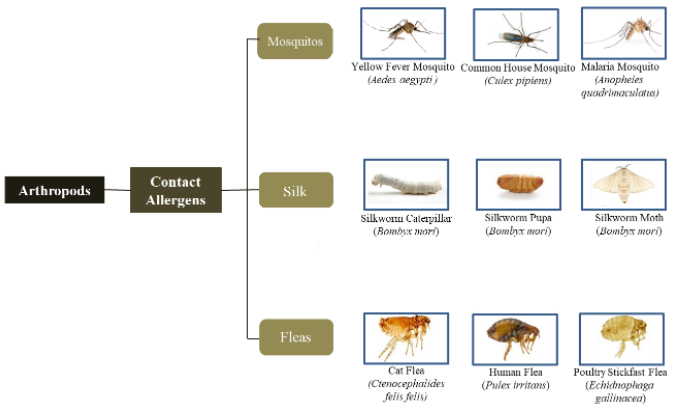

Fig. 8: Common arthropods species implicated in contact allergy.

Cockroach allergy has been reported as one of the most frequent environmental allergens in Pakistan (Abbas et al. 2015). Memona et al. (2017) conducted a collection-based survey and reported that *B. germanica* had the highest diversity indices and is the most dominant indoor cockroach species in Lahore, Pakistan. Furthermore, a survey-based study carried out in Southern Punjab, Pakistan revealed that about 80% people, who participated in the survey, were unaware of diseases transmitted by cockroaches (Naeem et al. 2014). A population-based study in Karachi, Pakistan concluded that out of 27 allergens tested on 88 individuals including children and adults, 33% exhibited moderate rates of reactivity to cockroach allergens, with 4.5% showed high reactivity rates (Abbas et al. 2015).

Clinical Manifestations

Cockroach allergens increase cellular penetration by disturbing the airway epithelial integrity, which not only leads to increased sensitization to cockroach allergen but also activates the innate immunity's cellular components such as dendritic cells, promoting Th2 response ultimately culminating in lung inflammation (Figure 7). Cockroach allergen sensitization is overwhelmingly associated with allergic respiratory distress, as well as development of asthma and asthma-like symptoms. Exposure to higher levels of cockroach allergens has greater asthma related hospitalizations and morbidities in cockroach antigen sensitized patients, especially in children. Studies show that a quarter of asthmatic children are sensitized to cockroach allergens (Rosenstreich et al. 1997; Stelmach et al. 2002.). Cockroach allergens responsible for asthma exacerbations are usually found in detectable levels in the house.

Cockroach allergen is a strong risk factor associated with severity and frequency of childhood allergies and asthma, especially in inner city residents, where higher cockroach infestations are recorded. Rates of emergency room visits, hospitalizations and days of school or work days missed are also higher in inner city residents, mostly due to cockroach allergen induced IgE levels (Gao 2012; Fukutomi and Kawakami 2021). Certain clinical markers, such as wheeze, inflammation and IgE monitoring, are potent indicators of sensitization to cockroach allergen and surrogate measure of the amount of exposure. The probability of cockroach allergen sensitization increases with increased exposure to the allergen. Sanitization often acts as a gateway to development of asthma and inflammatory respiratory diseases.

Prevention and Management

Exposure to cockroach allergen is of public health concern. Sufficient data suggests its association in the development of chronic respiratory diseases, such as asthma (Bourdin et al. 2009; Wang et al. 2021). Experts recommend eradication of cockroaches to reduce environmental allergens. A combination of pest management through pesticides, traps and general cleanliness, combined with patient and family education, are the effective approaches. Reservoir cleansing may be achieved through cleaning by using vacuum cleaners, washing of carpets, rugs and drapes with hot water and detergents. Professional cleaning and installation of HEPA filters can also reduce cockroach infestations.

Immunotherapy coupled with preventive measures can result in beneficial treatment for the sensitized patients. Several FDA standardized extracts are commercially available for immunotherapy; however their efficacy, besides in limited clinical trials, is debatable (Portnoy et al. 2013). There is no effective dosage and no standard symptom-based medications have so far been developed. However, placebo studies in India have shown significant clinical improvement after one year of immunotherapy (Srivastava et al. 2011).

Contact Allergens

Contact mediated irritation or allergic reaction to certain arthropods has been recorded as early as ancient Rome (Burgess 1993). Incidences of silk worm caterpillar allergy have existed as long as sericulture itself. Acute or chronic exposure to larvae, caterpillar or moth hairs cause irritation, usually followed by inflammation. The irritants are characterized either as histamines or soluble proteins which trigger histamine. Direct contact with larvae and caterpillar hair can cause permanent damage, such as when shed hair are blown due to wind and lodged in eyes. Arthropod contact allergens have seasonal density proportional to moth populations.

Occupational allergies associated with arthropods are well documented (Fukutomi and Kawakami 2021). Workers in arthropod breeding facilities, such as in laboratories, fly fishing farms and sericulture industry, routinely report contact allergies. Typical symptoms exhibited are rhiniconjunctival reactions, urticaria and asthma. Clinical symptoms develop rapidly in atopic individuals in comparison to non-atopic individuals. Specific IgE levels correspond to the levels of exposure to allergens. In most cases, patients are unaware of their allergies (Burgess 1993; Naeem et al. 2014).

Mosquitoes

Dermal inflammatory reactions to mosquito bites are common, especially in tropical and sub-tropical regions. However, anaphylactic reactions to mosquito bites are very rare (Larry 2002). A total of 19 proteins found in mosquito salivary gland extracts induce IgE mediated allergenic responses (Boorman 1987). Mosquito shedding, including wings, hair and feces, may become aerosolized and cause allergic reactions if inhaled. This is especially evident in occupational hazard studies, where workers are exposed to mosquitos such as when rearing mosquitos or when working in rice fields (Fukutomi and Kawakami 2021). Allergic reactions to inhaled mosquito allergens are typical hypersensitivity-I reactions, culminating in sneezing, dizziness, shortness of breath or even in some severe cases anaphylaxis (McCormack et al. 1995).

Positive skin prick tests using *Aedes* sp., *Culex* sp. and *Anopheles* sp. along with elevated specific IgE levels suggest sensitivity to these commonly found mosquito species. Immunotherapy has proved effective, however, it is not widely used and its effectiveness has not yet been clinically determined. Preventive measures include mosquito eradication or use of repellents. Evidence of natural desensitization due to repeated bites has also been recorded (McKiel and West 1961).

Silk Proteins

Allergic reaction to silkworm caterpillar (*Bombyx mori*) has been reported and many of its metabolites are now recognized as allergens capable of inducing severe hypersensitivity reactions (Suzuki et al. 1995). A recent study analyzed silkworm feces larva, pupa, moth and silk for potential allergens and identified 45 allergens. Furthermore, homology comparison analysis suggested cross-reactivity with several other arthropod allergens, including *Aedes aegypti*, *Dermatophagoides farinae*, *Malassezia furfur*, *Triticum aestivum* and *Tyrophagus putrescentiae* (He et al. 2021). Mounting evidence suggests that components of the silkworms cocoon and even silk pose allergic threat to sanitized populations.

Fleas

Fleas are quite common in occurrence, and infest humans and domestic animals. They are disease vectors and are responsible for transmission of pathogens and allergens (Souza 1997). Flea bites may induce hypersensitivity responses characterized as Flea Allergic Dermatitis (FAD), due to allergens present in the salivary glands (Halliwell 1984; Esch et al. 2001). Adult fleas are permanent ecto-parasites. This ensures continued longevity, a constant source of nutrition, reproductive opportunities and large egg production. Common fleas are shown in Figure 8.

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